VOLUME 39 NUMBER 4

ARCHIVES OF NEUROLOGY AND PSYCHIATRY

APRIL 1938

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00.

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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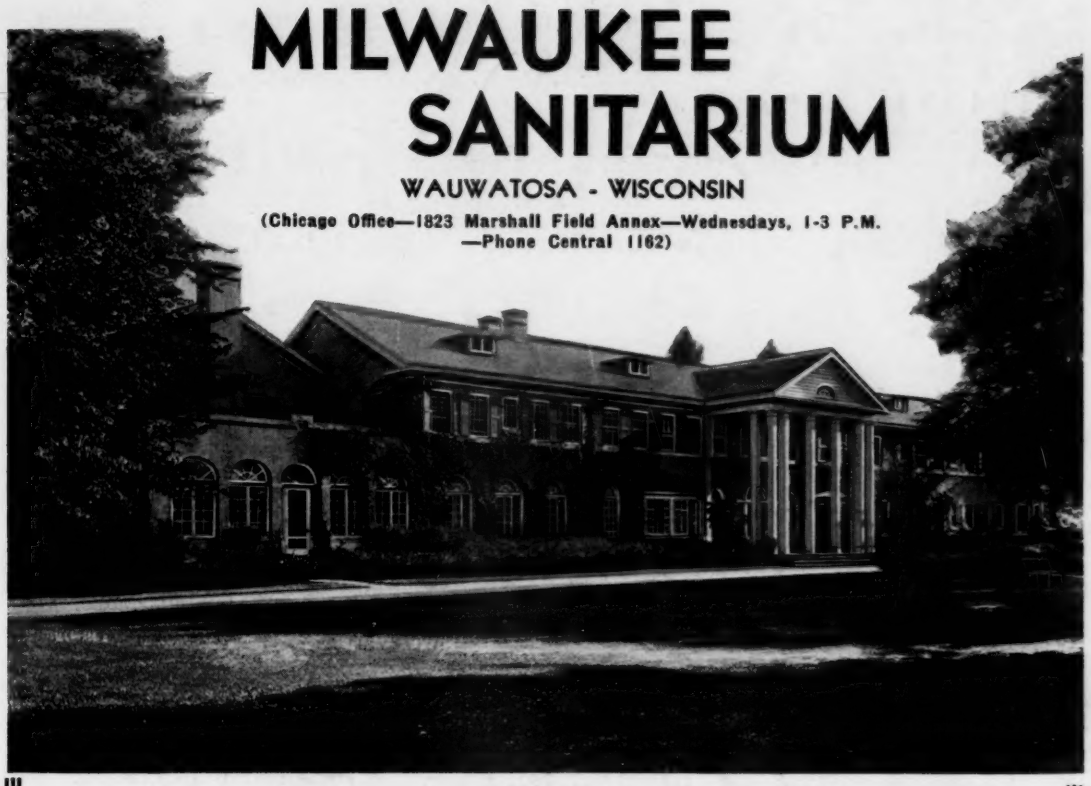

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VOLUME 39 APRIL 1938 NUMBER 4

PERIARTERITIS NODOSA

A CLINICOPATHOLOGIC STUDY WITH SPECIAL REFERENCE TO THE NERVOUS SYSTEM

JAMES W. KERNOHAN, M.D.

AND

HENRY W. WOLTMAN, M.D.

ROCHESTER, MINN.

Although one of the most constant clinical features of periarteritis nodosa is the presence of so-called neuritis and myositis, little attention has been paid to the pathologic changes in the peripheral or central nervous system. Every one recognizes that the changes which sometimes occur in the brain are the result of occluded arteries, with subsequent infarction of various portions of the cerebrum or cerebellum. Similar changes occur in the heart, kidneys and other organs of the body; yet it is not generally recognized that the changes which occur in the peripheral nervous system are actually the result of occluded nutrient arteries in the nerve trunks, with subsequent infarction of the nerve bundles. We have selected and studied the clinical records in five cases in which there were prominent neurologic symptoms and also have studied rather completely the neurologic tissues involved.

Since the examination of peripheral nerves in their entire length is impracticable as a routine, the degree to which disease of vessels may damage them is largely a matter of speculation and is probably underestimated. The problem is still further complicated by the amount of injury which associated toxins may inflict.[1] Just how extensive such damage may be is illustrated in the disease to which Kussmaul and Maier, in 1866,[2] gave the name "periarteritis nodosa." Since then,

Read at the Sixty-Third Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 3, 1937.

From the Sections on Pathologic Anatomy and Surgical Pathology (Dr. Kernohan) and the Section on Neurology (Dr. Woltman), of the Mayo Clinic.

1. (*a*) Baló, Joseph: Ueber eine Häufung von Periarteriitis-nodosa-Fällen, nebst Beiträgen zur Polyneuritis infolge von Periarteriitis nodosa, Virchows Arch. f. path. Anat. **259**:773-794, 1926. (*b*) Kimmelstiel, Paul: Beiträge zur Frage der Periarteriitis nodosa, ibid. **265**:16-30, 1927.

2. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. **1**:484-518, 1866.

about two hundred cases have been reported, but the incidence greatly exceeds the clinical and pathologic recognition.[3] The spontaneous development of this disease occurs also in pigs, dogs, deer and calves.[4] It has been suggested that the causative agent is a virus of the "rheumatic group," which either penetrates the intima of the vessel [5] or reaches it through the adventitial lymphatics.[3] Necrotizing panarteritis [6] results in thromboses, aneurysms and hemorrhages, all of which produce hybrid symptoms that are suggestive of many other diseases. This is the signal for possible periarteritis nodosa. The fact that a diagnosis has been made in about 15 per cent of cases, either from the clinical aspect alone or as a result of biopsy, suggests that a more general awareness of the illness will raise this percentage somewhat and provide more favorable opportunity for the discovery of satisfactory treatment.

The varied clinical picture is suggested by the general course of the illness, the organs most commonly involved and the erroneous diagnoses that have been made. The range of age extends from 3 months to 78 years; men are affected four times as often as women.[5] The average duration of the illness is from a few weeks to five months, but the disease may be fatal within one day or may last as long as six years. The mortality is from about 88 to 90 per cent.[7] Treatment is unsatisfactory, but preparations of arsenic may be tried.

The course is marked by exacerbations and new symptoms in varying situations. These may involve all organs of the body. The general appearance of the patient suggests a serious illness. The more common symptoms and findings include: fever; pallor; acceleration of the pulse; loss of weight; pain in and weakness of the extremities; renal and myocardial insufficiency; gastro-intestinal disturbances, such as pain, vomiting and bloody diarrhea; disturbances in vision, and cutaneous lesions. At any time life may be terminated by a complica-

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3. Middleton, W. S., and McCarter, J. C.: The Diagnosis of Periarteritis Nodosa, Am. J. M. Sc. **190**:291-308, 1935.

4. Baló, Joseph: Periarteriitis nodosa beim Hunde und vergleichende Untersuchungen über diese Erkrankung bei Menschen und Hunde, Virchows Arch. f. path. Anat. **248**:337-344, 1924. Nieberle: Zur Kenntnis der Periarteriitis nodosa bei Tieren, ibid. **256**:131-138, 1925.

5. Arkin, Aaron: A Clinical and Pathological Study of Periarteritis Nodosa: A Report of Five Cases, One Histologically Healed, Am. J. Path. **6**:401-426, 1930.

6. Krahulik, Lambert; Rosenthal, Maurice, and Loughlin, E. H.: Periarteritis Nodosa (Necrotizing Panarteritis) in Childhood with Meningeal Involvement: Report of a Case with Study of Pathologic Findings, Am. J. M. Sc. **190**:308-317, 1935.

7. Bernstein, Alan: Periarteritis Nodosa Without Peripheral Nodules Diagnosed Antemortem, Am. J. M. Sc. **190**:317-325, 1935.

tion, such as thrombosis, associated gangrene or hemorrhage or insufficiency of a vital organ.

The following organs are affected with especial frequency: the kidneys, in 80 per cent of cases; the heart, in 70 per cent; the liver, in 65 per cent; the gastrointestinal tract, in 50 per cent; the mesenteric artery, in 30 per cent; the muscles, in 30 per cent; the pancreas, in 25 per cent; the nerves, in 20 per cent, and the central nervous system, in 8 per cent.[5] Leukocytosis is present in 32 per cent of cases. The total number of leukocytes may reach 66,000 per cubic millimeter of blood, but the average number is from 15,000 to 30,000 per cubic millimeter. The percentage of eosinophils may reach 79; while eosinophilia is strongly suggestive of periarteritis nodosa, it is present in only 12 per cent of cases.[3]

The disease has been mistaken for trichinosis, myositis, purpura haemorrhagica,[3] typhoid, amebiasis, abscess of the liver, miliary tuberculosis, meningitis, tumor of the brain,[1a] alcoholic polyneuritis, lead neuritis and other conditions. The general clinical picture often includes cardiac and renal insufficiency and their accompanying laboratory data. In most cases there is hypertension.[7] The symptoms often have led to diagnosis through biopsy of the mesentery, muscle, gallbladder, appendix and kidney.

The neurologic symptoms are marked by extensive involvement of the peripheral nerves, especially those of the upper and lower extremities; there usually is a clinical picture of mononeuritis multiplex rather than one of multiple peripheral neuritis. Pain, tenderness of the nerve trunks and muscles, anesthesias, paralyses, loss of reflexes and atrophies occur in irregular distribution. Transient attacks of amblyopia and more permanent disturbance in vision may occur. Ophthalmoscopic examination may reveal thrombosis of the central artery, retinal and papillary edema, hemorrhages, detachment of the retina and the picture of albuminuric retinitis. There may also be diplopia, facial paralysis, loss of hearing and dysphagia. In one of the cases reported by Spiegel [8] the typical syndrome described by Ramsay Hunt developed. The meninges and brain [6] do not escape. There may be headache, vertigo, jacksonian and generalized convulsions,[9] decerebrate rigidity, masked facies,[10] conjugate deviation of the eyes, chorea,[11] movement

8. Spiegel, Rose: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**:993-1040 (Dec.) 1936.

9. Bennett, G. A., and Levine, S. A.: Two Cases of Periarteritis Nodosa: One with Unusual Manifestations (Meningeal Form), Am. J. M. Sc. **177**:853-859, 1929.

10. Fletcher, H. M.: Ueber die sogenannte Periarteriitis nodosa, Beitr. z. path. Anat. u. z. allg. Path. **11**:323-343, 1892.

11. Neale, A. V., and Whitfield, A. G. W.: Rheumatism and Its Relation to Arterial Disease and Periarteritis Nodosa, Brit. M. J. **2**:104-107 (July 21) 1934.

tremor, myoclonus, hiccup, hemiplegia, drowsiness, delirium,[7] mental dulness and coma.

The spinal fluid may be under increased pressure; there may be xanthochromia, cloudiness of the spinal fluid,[9] pleocytosis (1,280 neutrophils per cubic millimeter of fluid [8]) and an increase in the amount of globulin and total protein (100 mg. per hundred cubic centimeters [11]).

A large literature has accumulated on the subject of periarteritis nodosa. Most of the interest in the disease has been shown by pathologists, and many excellent descriptions of the gross and microscopic changes have appeared. Arkin suggested division of the characteristic changes in the small arteries into four stages. In the earliest, or acute, stage there is necrosis of the innermost part of the media of small arteries, which do not have any vasa vasorum, and of the outer portion of the media of large arteries, which have vasa vasorum. The second stage may be designated as the subacute phase; in this stage there is inflammation with exudate; eosinophils, lymphocytes, plasma cells and some polymorphonuclear leukocytes are present, and there is beginning proliferation of the fixed tissues around the vessels. Aneurysms or nodules may appear in this stage. Proliferation of the intima also occurs, and occlusion of the lumen and infarcts in various organs appear. The third stage, which may be termed the chronic phase of the disease, is characterized by the appearance of granulation tissue around the arteries and the beginning of healing. The fourth stage is really the phase of healing; this stage is not commonly encountered because patients who survive to this phase usually continue to live and microscopic studies are rarely carried out. This suggested classification of the stages of the disease as it occurs in the arteries helps greatly in understanding its progress, but, in reality, each so-called stage gradually merges into the subsequent one. In many cases several stages can be observed in one or several tissues or organs, which seems to us to explain the remissions and exacerbations to which patients suffering from periarteritis nodosa are subject.

Several other classifications of the disease have been suggested, such as that based on the organs, or system of organs, involved in the disease process, but neither this nor any of the other classifications has proved satisfactory. Excellent articles by Lorenz,[12] Meyer,[13] Schmincke [14] and many others have described periarteritis of the nutri-

12. Lorenz, Heinrich: Beitrag zur Kenntnis des multiplen degenerativen Neuritis, Ztschr. f. klin. Med. **18**:493-516, 1891.

13. Meyer, P. S.: Ueber die klinische Erkenntnis der Periarteriitis nodosa und ihre pathologisch-anatomischen Grundlagen, Berl. klin. Wchnschr. **58**:473-475 (May 9) 1921.

14. Schmincke: Ueber Neuritis bei Periarteriitis nodosa, Verhandl. d. deutsch. path. Gesellsch. **18**:287-293, 1921.

ent vessels to the nerves. In some of these studies there was marked degeneration of the nerve tissue, and in others the nerve tissue was almost normal. Wohlwill [15] described a case in which he observed marked degeneration of the nerve tissue but normal blood vessels; he expressed the opinion that the cause of the degeneration of the nerves was the same agent that produced the periarteritis nodosa in other organs. In a subsequent study he observed that the periarteritis involved the nutrient arteries of the nerves and accepted this as the cause of the degeneration of the nerves. He also said that in his previous case he had not completely examined the arteries. Degeneration of the brain and spinal cord as a result of occluded vessels in cases of periarteritis nodosa occurs less frequently than degeneration of most other organs of the body. Baló described two cases in which the cerebral vessels were involved in the inflammatory process and infarcts of the brain occurred subsequently. In his second case the central and peripheral nervous systems showed degeneration as the result of occlusion or partial occlusion of vessels. He expressed the belief that most of the changes in the nervous system are the result of lesions in the vessels, but he said also that in some cases, especially those in which the disease is very acute, the toxins which affect the arteries affect also the nerves. Marinesco and Draganesco [16] also carefully and thoroughly described a case of periarteritis nodosa in which the disease involved the vessels supplying the peripheral nerves, nerve roots, spinal cord and brain. In a few cases which have been reported in the literature, pathologic changes have occurred in the eyes. Müller [17] was the first to describe the histologic changes in the small vessels of the retina; these lesions were the same as those in the arteries in the substance of the brain. Goldstein and Wexler [18] reported the second case in which these changes were described. In this case the retina was normal, but there were early changes in the media of the arterioles of the choroid of the eye. No changes had been noted in the eye on ophthalmoscopic examination. We have been unable to find a report of any other case in which the microscopic changes in the eyes were described. The entire literature on periarteritis nodosa is voluminous; so this review is, of necessity, short and incomplete.

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15. Wohlwill, F.: Fall von Periarteriitis nodosa, Deutsche med. Wchnschr. **1**:366 (March 28) 1918; Ueber die nur mikroskopisch erkennbare Form der Periarteriitis nodosa, Virchows Arch. f. path. Anat. **246**:377-411, 1923.

16. Marinesco, G., and Draganesco, S.: Sur la forme myélo-neuro-myopathique de la maladie de Kussmaul, Ann. de méd. **22**:154-171, 1927.

17. Müller, P., cited by Goldstein and Wexler.[18]

18. Goldstein, Isadore, and Wexler, David: The Ocular Pathology of Periarteritis Nodosa, Arch. Ophth. **2**:288-299 (Sept.) 1929.

REPORT OF CASES

CASE 1.—*History.*—A farmer aged 54 came to the Mayo Clinic on Jan. 25, 1937, because of weakness. One morning in 1931 he had painted his automobile with shellac. On the same afternoon numbness and tingling had appeared in the tips of the fingers and had spread to a point midway between the elbows and the shoulders. A day or two later similar paresthesias had started in the toes of both feet and had extended to the middle of the thighs. Associated with this there had been weakness and tenderness of the muscles of the extremities. The patient had been helpless for ten weeks, but he gradually had made a complete recovery. He had remained well until February 1936, when he had what he believed to be an ordinary cold. During the first week in November 1936 he had painted a fence. Soon after this he had noticed weakness in the legs, and by November 7 he had crawling paresthesias in the limbs and face. There also had been dull pains, punctuated with lightning pains, in the limbs and head. The extremities had become progressively weaker, and by Jan. 8, 1937, he had had to go to bed. On January 14 he had noted difficulty in swallowing; by January 23 this had become so extreme that a nasal tube had been inserted for feeding.

Examination.—The patient was well developed and well nourished. He spoke in a whisper. There were horizontal nystagmus and loss of convergent accommodation of the left eye. The retinal veins were engorged and mildly cyanotic. The right half of the palate and tongue and the right sternocleidomastoid and trapezius muscles were weak. The right vocal cord was fixed in the midline, and the range of movement of the left vocal cord was about 50 per cent of the normal. The pharyngeal muscles were paretic. The left half of the diaphragm was paralyzed. The lower extremities and distal portions of the upper extremities were completely paralyzed. Some movement remained in the muscles of the shoulder girdle. All tendon reflexes were absent. Appreciation of pain was slightly impaired in the hands and feet. Vibratory and postural sensibility was completely lost in the hands and feet. There was marked tenderness of the muscles. No response to plantar stimulation was obtained.

Urinalysis did not reveal any abnormality. The concentration of hemoglobin was 14.7 Gm. per hundred cubic centimeters of blood. There were 4,230,000 erythrocytes and 10,500 leukocytes in each cubic millimeter of blood. Examination of a blood smear did not reveal any abnormality. Flocculation tests for syphilis gave negative results. The value for urea was 42 mg., and that for sugar, 134 mg. per hundred cubic centimeters of blood, and that for chlorides, 602 mg. per hundred cubic centimeters of plasma. Analysis of a twenty-four hour specimen of urine revealed no lead or arsenic. The spinal fluid was under an initial pressure of 15 cm. of water; the subarachnoid communications were free; the Kline and Kolmer tests gave negative results, and there was 1 small lymphocyte in each cubic millimeter of the fluid. The value for protein was 50 mg. per hundred cubic centimeters of fluid; the Nonne-Apelt reaction was positive, and there were 103 mg. of sugar and 726 mg. of chlorides in each hundred cubic centimeters of the fluid. The sedimentation rate of the erythrocytes was 76 mm. in one hour.

Course.—In the five days that the patient was in the hospital the axillary temperature gradually rose to 101.6 F. The average pulse rate was 110 beats per minute. At about 11:30 a. m. on January 29, the patient rather suddenly became dyspneic and cyanotic and broke into a profuse perspiration; he died early in the afternoon of the same day.

Autopsy.—The only gross lesions observed at necropsy were edema of the vocal cords and beginning bronchopneumonia of the lower lobe of the right lung. The

brain and spinal cord appeared normal, and there were no nodules or thickening of any vessels of the base of the brain or any of their branches. No gross changes in any of the large nerve trunks of the body or in the smaller nerves of the legs were observed, and there were no nodules on the coronary, renal or mesenteric arteries. The heart, kidneys, liver and gastro-intestinal tract were normal.

Microscopic examination of many sections of all organs of the body showed that the arteries and arterioles were normal. There was no endarteritis, mesarteritis, or periarteritis of any vessel, except one small artery in the posterior portion of the capsule of the prostate. This vessel was in close proximity to the plexus of the sympathetic nerves in the posterior portion of the prostatic capsule, below the seminal vesicles. Microscopic sections were made of both sciatic and femoral nerves, the various nerves composing the brachial plexus, the right posterior tibial nerve, the phrenic nerves, several intercostal nerves, several anterior and posterior nerve roots of the spinal cord and several dorsal root ganglia. All these sections were studied with hematoxylin and eosin, Van Gieson's stain, Weigert's elastic stain, Perdrau's silver impregnation method, Weigert's myelin sheath stain, the Mallory-Heidenhain stain, scarlet red and a modified silver impregnation method for staining axis-cylinders.

Examination of sections of the right sciatic nerve showed that the larger vessels of the nerve had undergone a characteristic necrotic inflammatory reaction. The most profound change had taken place in the inner half of the media, which had a peculiar hyaline necrotic appearance. It stained homogeneous pink with eosin, but was fragmented and clumped. The outer half of the media was partly degenerated, but not necrotic. The muscle fibers were separated and edematous, and the nuclei were pale and stained poorly, as is the characteristic appearance of most degenerating tissues. The adventitia, which radiated from the walls of the arteries, was prominent and much more dense than normal, since it was infiltrated with lymphocytes, plasma cells and many large endothelial-like cells. There were a few eosinophils; but no polymorphonuclear leukocytes. At a greater distance from the arteries most of the inflammatory cells were lymphocytes, but there were a few plasma cells and endothelial cells, some of which were undergoing mitotic division. Many small dilated vessels, which we considered capillaries, were present in the thickened adventitia, giving it the appearance of granulation tissue. The intima of the arterioles was separated from the media, and the space between contained some lymphocytes, plasma cells and many endothelial cells. This entire process had reduced the lumens of the involved vessels to varying degrees, usually to less than half the normal diameter; there sometimes was almost complete obliteration of the vessels. The Van Gieson stain showed that there was no increase in connective tissue and that the inner half of the media was necrotic, with few normal muscle fibers. The Weigert elastic stain showed that most of the internal elastic lamina had disappeared and that the remaining portion was split into numerous fine strands. These were separated, and the spaces between were filled with cells.

Almost all the larger vessels in the connective tissue between the nerve bundles were involved in the inflammatory degenerative process; however, some were normal. None of the smaller arteries or arterioles were inflamed or degenerated. Study of the nerve bundles revealed edema, especially beneath the perineurium, but also in several places throughout the bundles. There was almost complete absence of inflammatory cells, but some scavenger cells containing fat droplets were present along the course of the fibers. The cells of the sheath of Schwann were markedly increased in number, but we were unable to observe any mitotic figures in these cells. The blood vessels in the nerve bundles were normal, except

that all were dilated. Myelin sheath stains revealed that some nerve bundles were almost normal while others were almost completely destroyed and only a few scattered myelin sheaths remained (fig. 1 *A*). In longitudinal sections of the nerve it was seen that many myelin sheaths had been destroyed and had disappeared; some were normal, while others were undergoing degeneration, as evidenced by the swelling, beading and fragmentation of the myelin (fig. 1 *B*). The silver impregnation method demonstrated that most of the axis-cylinders had disappeared; some were normal, and others were undergoing degeneration and were swollen, nodular, beaded, vacuolated and fragmented.

Sections through this sciatic nerve did not all show the same changes in the blood vessels. Examination of one cross section, which was obtained about 1 inch (2.5 cm.) below the section which has just been described, showed that all the arteries were normal. Degeneration of the myelin, on the other hand, was more extensive, and it was with difficulty that a normal myelin sheath was found in some nerve bundles, while the myelin sheaths of others appeared almost normal.

The right posterior tibial nerve did not contain any arteries similar to those observed in the sciatic nerve, but the lesions in some nerve bundles varied from marked degeneration to almost complete disappearance of the myelin sheaths and axis-cylinders, while the appearance of others was almost normal. There was no inflammation in the nerve bundles and none in the perineurium, which was not increased. There were some edema of the nerve bundles and an increase in the sheath of Schwann cells. The anterior and posterior nerve roots within the dura mater on the right side of the lumbar portion of the spinal cord were edematous, but were otherwise unaffected. The blood vessels accompanying these nerve roots were normal.

The left sciatic nerve was similar to that on the right. The nutrient arteries in the nerve had undergone a subacute inflammatory process, which was accompanied by necrosis of the inner portion of the media. The lumens of these vessels were narrowed and in some instances almost obliterated. The nerve bundles varied considerably; some showed extensive degeneration of the myelin sheaths and axis-cylinders, which was accompanied by proliferation of the sheath of Schwann cells. There was no inflammatory reaction within the perineurium, but there was edema of the nerve bundles.

The femoral nerve on this side was similar to the sciatic nerve in that several of the arteries showed a subacute inflammatory process and partial obliteration; the nerve bundles also had undergone degeneration, and there was marked edema. No inflammation was seen inside the perineurium, but there was an increase in the number of the sheath of Schwann cells. The nerve bundles of the brachial plexus showed changes similar to those in the sciatic nerves, except that they were less pronounced. The changes in the nutrient arteries were subacute and pronounced; fewer vessels, however, were involved, and more were normal. However, there were marked edema of the nerve bundles and extensive degeneration of the myelin sheaths and axis-cylinders, which was even more pronounced than in the sciatic nerves. There was slight inflammation in the nerve bundles, as evidenced by the presence of lymphocytes; in places these were collected into small groups, and the sheath of Schwann cells had undergone proliferation. The axis-cylinders showed no evidence of regeneration.

Microscopic sections taken at different levels of the nerves showed marked variation in the inflammatory processes in the arterioles. In some sections almost every artery was involved in the process, while in others most of the arteries were normal. The veins were free from inflammation, and all vessels in the nerve bundles were patent and dilated, as they were in the sciatic nerves.

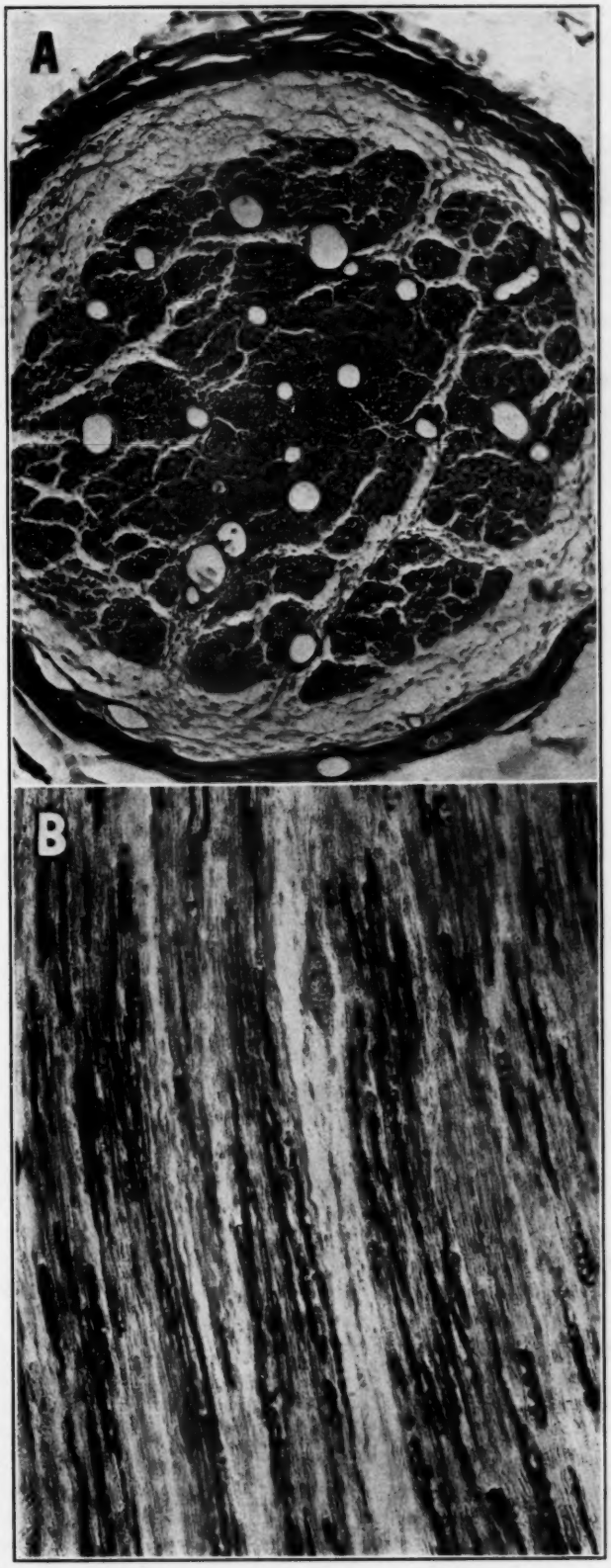

Fig. 1.—Sections of a peripheral nerve (Weigert's myelin sheath stain). *A*, marked edema between the nerve tissue and the epineurium. The blood vessels (mostly veins) are widely dilated, and the myelin sheaths are degenerated; × 105. *B*, extensive degeneration of myelin sheaths. Some of the sheaths have disappeared, while others are undergoing degeneration; there is edema between some of the nerve fibers; × 150.

Examination of various portions of the sympathetic nervous system showed that all the nerves and ganglion cells were normal for a man of the age of the patient. The nerve cells and fibers in the dorsal root ganglia were normal, as were the arteries in and around the ganglia.

The phrenic and recurrent laryngeal nerves were normal.

The brain and spinal cord were normal except for early acute changes in the nerve cells in the middle convolution of the right frontal lobe. A similar change was observed in the nerve cells of the nuclei of the eighth and twelfth cranial nerves in the medulla oblongata. All the arteries of the brain and spinal cord were normal.

This case is unique in that the periarteritis nodosa was limited to the nerve trunks of the upper and lower limbs. Careful examination of all other organs of the body failed to reveal a single vascular lesion, except in one artery in the capsule of the prostate gland. We were not able to find any reason that the lesions should be so strictly limited to the nerves. In the peripheral nerves they were extremely widespread. Most of the lesions were remarkably uniform and were limited to the very early and the subacute stages. This observation corresponds with the clinical history, which was comparatively short for the disease entity.

Case 2.—*History.*—A man aged 39 had had attacks of epigastric distress, which usually lasted two or three weeks. For ten years, particularly in the spring and fall, these attacks had come with regularity, except on one occasion when he had been in the mountains and had worked hard. During the three months before he came to the clinic the pain had been more or less continuous, although not severe, and he had lost about 20 pounds (9 Kg.). He also had been troubled with bleeding hemorrhoids.

Examination.—The appearance was that of a fairly well nourished and healthy man. The systolic blood pressure was 112 mm. of mercury, and the diastolic pressure, 80 mm. There were external hemorrhoids of moderate size. The number of leukocytes was 12,100 per cubic millimeter of blood. Analysis of the gastric contents showed a total acidity of 54 degrees and free hydrochloric acid of 38 degrees, according to the method of Töpfer. Roentgenograms of the stomach disclosed a duodenal ulcer which had a central crater. Operation, which was performed on Nov. 24, 1930, revealed an ulcer on the anterior wall of the duodenum, 1 inch (2.5 cm.) below the pylorus. Posterior gastro-enterostomy and appendectomy were performed.

Course.—After the operation the patient made an uneventful recovery; he remained well for three months and gained 25 pounds (11.3 Kg.).

In February 1931 a dull, steady, aching pain appeared in the suboccipital region. On March 10, for some unexplainable reason, the patient could not "keep on walking without collapsing." On March 14 he had a sore throat, and pain appeared in both legs, chiefly in the calves, when in the dependent position. On March 16 there were pains in all joints. Treatment for rheumatism produced improvement, and the patient was up and about from May 15 to June 15. Pitting edema then developed, especially in the evening. By June 20 he was kept awake by severe shooting pains in both feet and arms. The distal parts of the four extremities became the seat of hyperesthesias, and anesthesia and weakness appeared subse-

quently, especially in the fourth and fifth digits of the left hand. On July 20 he became short of breath, coughed a good deal and raised bloody sputum. Since March he had had occasional attacks of fever, which was as high as 103 F.; he had lost 23 pounds (10.4 Kg.) and had become extremely weak.

The systolic blood pressure was 180 mm. of mercury, and the diastolic pressure, 110 mm. There was slight enlargement of the cervical lymph nodes. The cervical portion of the spinal column was somewhat tender, and the extremities were painful when moved or touched. The left border of the heart was extended 1 inch (2.5 cm.) beyond the nipple line, and there was a soft systolic murmur.

The liver was just palpable. Rales and dulness were present in the bases of both lungs. On August 1 vision appeared to be normal; there was some hyperemia of the optic disks; the margins of the optic disks were blurred, and a few hemorrhages and "cotton wool" patches were present in the retina. The retinitis was said to be suggestive of a septic condition. Urinary findings indicated glomerular nephritis. There was slight weakness of the muscles of the hands, legs and feet, especially of the right anterior tibial and peroneal muscles. The patellar reflexes were diminished, particularly on the right side, and the achilles tendon reflex was absent on both sides. The dorsum of the right foot was anesthetic; superficial sensibility of the fingers and toes was slightly diminished, and there was slight astereognosis in the left hand. The ulnar and peroneal nerves were slightly indurated, enlarged and sensitive. A diagnosis was made of mild generalized peripheral neuritis.

Examination on August 17 disclosed bilateral foot drop, loss of the achilles tendon reflex on both sides and a tendency to wrist drop. The findings noted on examination of the thorax were interpreted as indicating congestion; the edge of the liver extended 1 inch (2.5 cm.) below the costal margin. The general condition suggested septicemia with secondary nephritis and cardiac decompensation.

By August 5 two blood cultures had proved sterile. On August 6 paralysis of the right side of the diaphragm was noted. On August 7 examination of the urine disclosed 3.7 mg. of arsenic and 0.04 mg. of lead in 1,500 cc. of urine. On August 14 there was respiration of the Cheyne-Stokes type. The possibilities of arsenic and lead poisoning, beriberi, tuberculosis, amebiasis, abscess of the liver and mediastinitis were considered. On August 17 there was difficulty in voiding urine, and the patient admitted that he had had gonococcic urethritis. On August 18 he became dyspneic, coughed up a good deal of bloody, mucoid sputum and became somewhat stuporous. On August 19 the bladder became distended. The right upper quadrant of the abdomen was extremely tender, and the patient screamed with pain whenever he swallowed a small amount of fluid. The blood pressure remained at about 174 mm. of mercury systolic and 120 mm. diastolic. The urea content of the blood increased gradually to 132 mg. per hundred cubic centimeters. The patient became comatose; there was muscular twitching, and he died on August 20.

During the three weeks that the patient was in the hospital the temperature did not exceed 101 F.; the pulse rate averaged 100 beats per minute and reached peaks at 120. During the last week in the hospital the output of urine gradually decreased, in spite of a maintained intake of fluid. On many occasions analysis of the urine disclosed a moderate amount of albumin; there were sometimes hyaline and granular casts, erythrocytes and leukocytes. The concentration of hemoglobin in the blood remained in the neighborhood of 60 per cent. The number of erythrocytes was about 3,600,000 per cubic millimeter of blood, and the number of leukocytes increased gradually from 14,800 to 20,400 per cubic millimeter. Examination of the blood smear revealed slight anisocytosis, poikilocytosis and slight

evidence of toxemia. The Wassermann reaction of the blood was negative. Three blood cultures were sterile. Examinations of the stools disclosed blood. Agglutination tests gave negative reactions for undulant fever, typhoid and paratyphoid. Numerous other tests did not disclose anything of importance.

Necropsy.—The heart was hypertrophied as the result of hypertension, and there was healed rheumatic endocarditis of the mitral valve. The lungs were the site of many infarcts, with bronchopneumonia, and the kidneys were atrophic and contained many scars, as well as many recent infarcts. A gastro-enterostomy had been performed for relief from a duodenal ulcer, which had healed; only the scar of the ulcer remained. Chronic passive congestion of the liver and slight enlargement of the spleen were noted. There were no aneurysmal dilatations or nodules along the course of any of the coronary, mesenteric or renal arteries or of any small artery which we could examine. No gross lesion was visible in any of the vessels of the peripheral nerves. The cause of death was considered to be malignant hypertension, arteriosclerotic and arteriolosclerotic atrophy of the kidneys and uremia. Permission was not granted for examination of the brain or the spinal cord.

Microscopic examination showed widespread periarteritis nodosa of all organs except the thymus and the skin. The small arteries in the lungs were least involved, while the vessels of the heart, kidneys, liver, pancreas, adrenal glands, prostate gland and testes were extensively inflamed. The inflammation was, for the most part, in the periarterial connective tissues; in some small arteries it was more acute and more extensive, while in others the inflammation had almost completely subsided and left marked fibrosis of the walls and a narrow lumen. Most organs had undergone considerable parenchymatous degeneration as the result of the reduced blood supply, and, in consequence, excessive amounts of fibrous tissue were present

The peripheral nervous system was examined by using the same technical methods as those in case 1. The changes in the left sciatic nerve were almost identical with those described in the first case, but there were several places in which the lesions differed and the apparent age of the lesions varied. Examination of a few small arteries showed hyaline-like necrosis of the inner half of the media. The inflammation in the outer half of the media and of the adventitia was of recent origin, since some polymorphonuclear leukocytes were present. There were, in addition, many lymphocytes, plasma cells and endothelial cells as well as proliferating connective tissue. The internal elastic lamina had almost completely disappeared, and the portions which remained were fragmented. Some vessels showed subacute inflammation, and in several the inflammatory processes had almost completely subsided and much fibrous tissue had replaced the media and the adventitia, which was very thick. One change was common to all the vessels; that is, the lumen was markedly reduced, and in some vessels completely obliterated. Examination of sections of the nerve, obtained 2 inches (5 cm.) above the section described previously, showed that all the arteries and arterioles were normal. The nerve bundles at this level were also normal except for slight edema. As a fact, even at the level at which the vessels were most severely inflamed the nerve bundles were well preserved, in spite of marked edema and some degeneration of the myelin sheaths. There was no inflammation in any of the nerve bundles. Two inches (5 cm.) below the level at which the arteries were most inflamed there was profound degeneration of almost all the myelin sheaths and axis-cylinders. Less than 5 per cent of the myelin sheaths were normal. Numerous infarcts of the nerve bundles were present at this level. The degenerative processes

were similar to those described in case 1, except that in many nerve bundles they were more advanced. As in the first case, no inflammation of the nerve bundles was present.

In sections of the right sciatic nerve, none of the small arteries showed evidence of the acute stage of the arteritis. All showed evidence of subacute and chronic inflammation, but we did not observe any arteries in which the inflammation was completely quiescent and in which only dense connective tissue could be seen. The internal elastic lamina was present in all vessels, but was split into many fine strands. We thought that in some vessels there was an actual increase in the

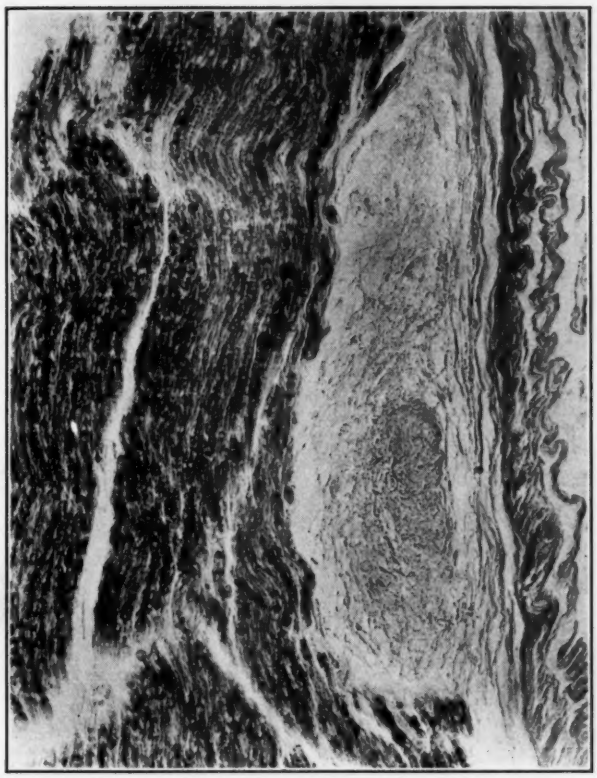

Fig. 2.—Small solitary, but clearly outlined, infarct beneath the epineurium of a peripheral nerve. Weigert's myelin sheath stain; × 145.

amount of the elastic tissue. At the level at which the arterial lesions were most profound the myelin sheaths were well preserved, except for several infarcts (fig. 2). However, there was marked edema, particularly of the tissue immediately beneath the perineurium. At levels below this there was extensive degeneration of the myelin sheaths and axis-cylinders, which was associated with proliferation of the sheath of Schwann cells, but no inflammation was present in the nerve bundles.

In the left femoral nerve the small arteries had thick, fibrous walls. There were an excess of elastic tissue and some periarteritis, but this was chronic and was subsiding. All the arterioles had been involved in the process, which seemed everywhere to be at about the same stage of healing. In all the vessels the walls

were extremely thick and the lumens narrow. In the nerve bundles the degeneration was more extensive than that in any nerve which we have so far examined. All elements were degenerated except the sheath of Schwann cells, which were increased in number. There was no inflammation in any of the nerve bundles.

The right femoral nerve was almost normal in the various sections which we examined. There was some edema, but no degeneration, of the nerve bundles. The small arteries had thick walls; no inflammation, however, was seen in the media or adventitia, and there was no proliferation of the intima. We considered the change in the walls of the arteries as secondary to the severe hypertension.

In the brachial plexus the inflammatory lesions of the small arteries were in all the stages of evolution which we have described (fig. 3 *A* and *B*). In one of the larger arteries the lumen had been completely occluded and was recanalized (fig. 4). Narrowing of the lumens of the arterioles was observed in all stages of the inflammation, being less marked in the acute, early stage and most marked in the chronic or healing stage. There was extensive degeneration of almost all the nerve bundles; some were more degenerated than others, and there were many infarcts. Some of the infarcts were small (fig. 2) and others large; in some places they had become confluent and produced profound and widespread degeneration. There was no inflammation in any of the nerve bundles, but the number of Schwann cells was markedly increased.

There were no occluded vessels inside the epineurium of any of the nerve bundles; rather, the contrary held true, as almost all vessels in the branches of the nerves were widely dilated.

This case was a typical instance of widespread periarteritis nodosa, except that there were no aneurysms or nodules along the course of the smaller arteries. However, the absence of these changes is a common observation in the disease; the occurrence of aneurysms is the exception rather than the rule. The presence of multiple infarcts in the nerve bundles supports the idea that the so-called neuritis is the result of inadequate blood supply rather than of toxic action on the part of the agent which produces the arteritis.

CASE 3.—*History.*—A skilled laborer aged 36, who came to the clinic for examination on May 31, 1926, had had influenza in 1918 and gonococcic urethritis in 1924. About the middle of February 1926 weakness had appeared in the arms and legs; this had been associated with severe pain and tenderness. Two weeks later he had suffered from severe abdominal cramps and marked constipation. These pains often had kept him awake at night and had been accompanied by tenderness of the abdomen, particularly over the right hypochondrium. He had lost 35 pounds (15.9 Kg.). Toward the end of April persistent tingling paresthesias had appeared in the right hand and foot. He had often been exposed to paint and had not taken care to wash his hands before eating.

Examination.—The patient was somewhat emaciated. The systolic blood pressure was 138 mm. of mercury, and the diastolic pressure, 100 mm. There were moderate weakness and corresponding atrophy of the muscles of the hands, forearms and arms, but there was no atrophy of the shoulder girdle. The biceps reflex was absent, and the triceps and supinator reflexes were diminished. The patient was able to walk rather well. The patellar and achilles tendon reflexes on both sides were much impaired. Marked muscular tenderness was noted; this exceeded the

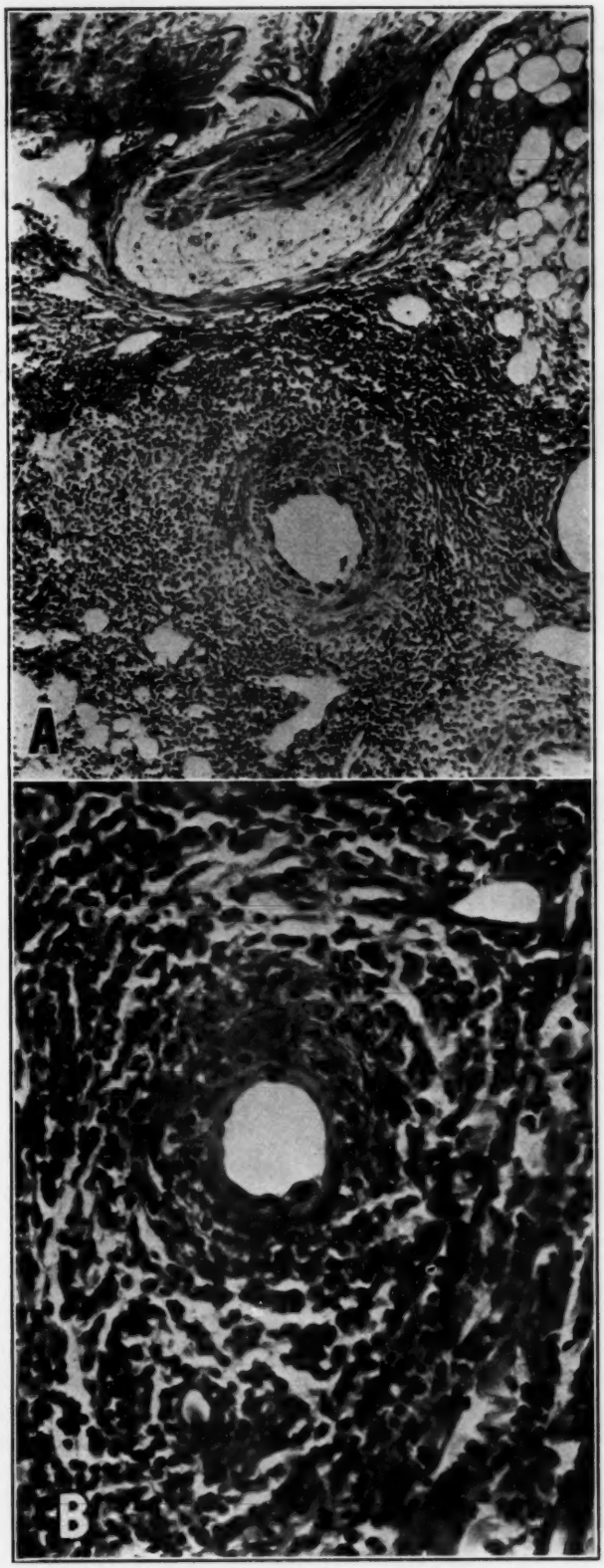

Fig. 3.—*A*, edema around one of the nerve bundles. The small artery has marked periarteritis in the subacute stage; there are lymphocytes in the media, which is diminished. Hematoxylin and eosin stain; × 90. *B*, almost complete destruction of the media of a small artery. The stage of periarteritis is between the subacute and the chronic phase, but the inflammatory process in the media is subacute and there are many polymorphonuclear leukocytes; there is as yet no proliferation of the intima. Hematoxylin and eosin; × 275.

tenderness of the nerve trunks. The patient was emotional, inattentive and irritable. A diagnosis of multiple neuritis, possibly due to lead, was considered.

Course.—At times there was slight elevation in the temperature and pulse rate. Urinalysis did not disclose any abnormality except a faint trace of albumin and an occasional hyaline cast, erythrocyte or leukocyte. The concentration of hemoglobin in the blood was 40 per cent. The erythrocytes numbered 3,080,000, and the leukocytes, 11,500 per cubic millimeter of blood. A differential blood count showed nothing unusual; the percentage of eosinophils was 1.5. The leukocytosis increased gradually, and by June 15 there were 22,000 leukocytes per cubic

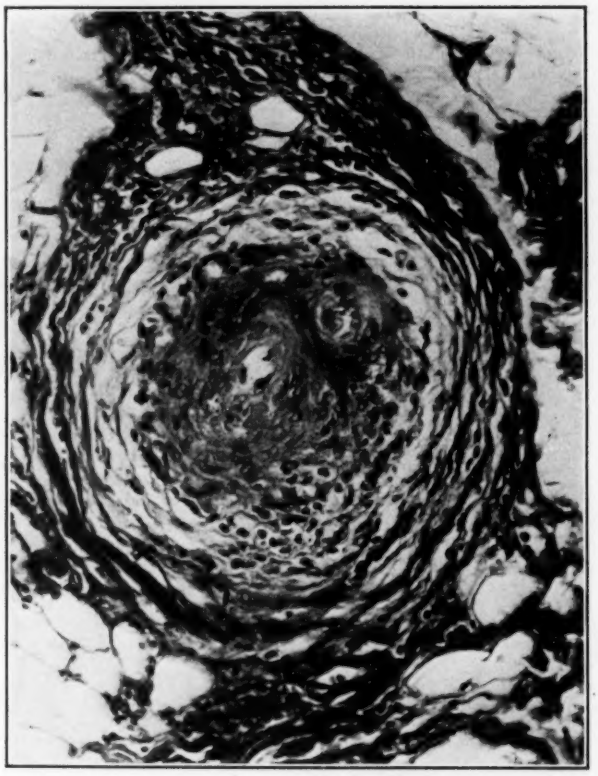

Fig. 4.—Small artery of a peripheral nerve, showing almost healed periarteritis nodosa with only a few lymphocytes in the adventitia. The lumen has been obliterated and is recanalized. Hematoxylin and eosin stain; × 220.

millimeter of blood. Slight anisocytosis and polychromatophilia and very slight basophilic stippling were present. Analysis of the gastric contents disclosed total acidity of 38 degrees and free hydrochloric acid of 14 degrees, according to the method of Töpfer. Roentgenograms of the stomach showed nothing abnormal. On June 3 the Wassermann reaction of the blood was strongly positive; on June 5, weakly positive, and on June 8, strongly positive. Urinalysis on June 7 did not reveal lead or arsenic; on June 14 there were 1 mg. of arsenic per hundred cubic centimeters of urine and a faint trace of lead, and on June 16 there was no arsenic but a faint trace of lead. Two blood cultures were sterile. The value for the bilirubin content of the serum by direct reaction was 5.6 mg. per hundred cubic centimeters. Roentgenographic examination of the thorax on June 6 showed

a moderate degree of enlargement of the heart and infiltration of both lungs, which suggested pneumonia. The patient expectorated small amounts of blood, and the pulse became rapid and of poor quality. Examination of the eyegrounds did not disclose any abnormality. On June 7 there was marked cyanosis of the lips, and the facies became pinched and gray. Some cardiac enlargement, a gallop rhythm and findings that suggested a toxic or infectious factor and the possibility of intracardiac thrombosis were noted. Gross examination of the stools revealed the presence of blood. Other laboratory tests gave little added information. On two occasions during the three weeks that the patient was in the hospital the temperature rose, once to 100 F. and again to 101 F. The pulse rate averaged about 120 beats per minute. The patient became progressively weaker and died on June 20.

Necropsy.—The heart was hypertrophied as a result of hypertension; there were no nodules along the course of any of the coronary arteries and no infarcts in the myocardium. There were several small, closely adherent mural thrombi in each auricle. Several small infarcts were present in the lungs; some were of recent origin and hemorrhagic, while others were much older and less hemorrhagic and showed organization. Extensive bronchopneumonia was present in both lungs. The spleen was slightly enlarged, probably as the result of chronic passive congestion. Chronic passive congestion of the liver and necrosis of the centers of the lobules also were noted. There were several small ulcers in the ileum and small hemorrhages beneath the mucosa. The surfaces of the kidneys were deeply pitted with numerous old and recent infarcts. No gross changes were observed in any of the other organs. The brain and spinal cord did not show any gross abnormality. As many of the peripheral nerves as possible were removed, but no gross lesion was observed in any of them.

Microscopic study of the various organs showed extensive periarteritis nodosa of practically every organ. The inflammatory process in most of the vessels, except those of the lungs and gastrointestinal tract, was almost healed, and the lumens of these vessels were much narrowed and in places almost obliterated. In the lungs and gastrointestinal tract the vascular lesions consisted of hyaline-like necrosis of the inner portion of the media of very small arteries. Associated with this medial degeneration were many polymorphonuclear leukocytes, but no lymphocytes or plasma cells; there was no periarteritis. The lumen of many of these vessels was almost obliterated. The blood vessels of the central nervous system were normal, as was the central nervous system itself. There was periarteritis nodosa of most of the nutrient arteries in the trunks of the peripheral nerves. This was either in the acute stage, and associated with necrosis of the media, or in the chronic stage, and associated with beginning fibrosis of the media and proliferation of the intima, which resulted in partial or almost complete obliteration of the lumen of the vessel. There was also well marked chronic periarteritis. We did not see any vessel in which there was healed periarteritis similar to that in the small arteries of the kidneys; however, some arteries showed several intermediate stages between the acute and the chronic form of the disease. Not all vessels in the nerves were involved in the inflammatory degenerative process, as some were normal (fig. 5). In the more proximal portions the nerve bundles were normal, but at a short distance below the partially or completely obliterated arteries degeneration of the myelin sheaths and axis-cylinders was marked; in the same regions there was an increase in the number of cells belonging to the sheath of Schwann.

Microscopic study of portions of the sympathetic nervous system revealed that it was normal except for a small part of the celiac ganglion. All the small

arteries around this ganglion had thick, fibrous walls and narrow lumens, but there was practically no inflammatory reaction. Several of the nerve bundles emerging from the ganglion were much degenerated; yet the nerve cells themselves were intact and normal, except for a small number underneath the capsule at one place.

This case illustrates the histologic variations in the small arteries associated with periarteritis nodosa (fig. 5). Some arteries were in the acute stage of the disease, and in others the inflammatory process

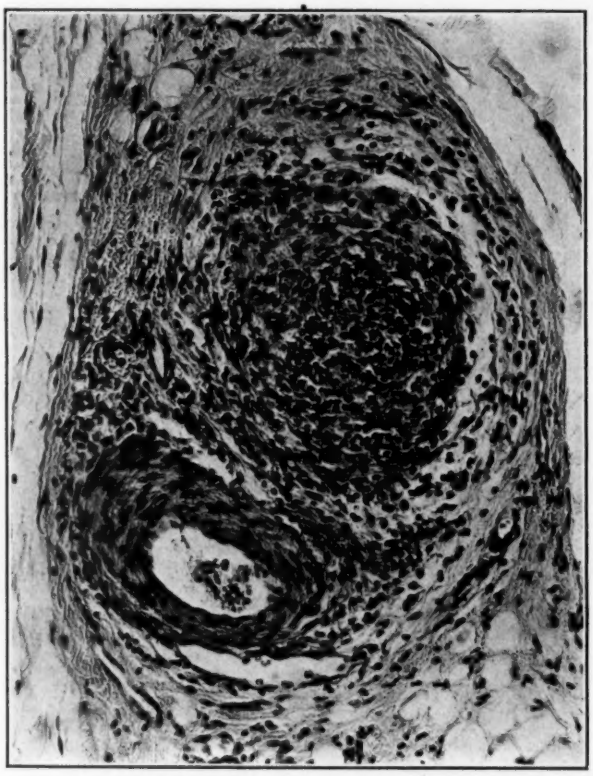

Fig. 5.—Two vessels in a peripheral nerve. One is almost normal, and the other has been obliterated by periarteritis nodosa in a stage between the subacute and the chronic phase. Hematoxylin and eosin stain; × 175.

had subsided. The changes in the arteries in this case did not suggest those due to syphilis, lead or arsenic; the amount of lead and arsenic present in the body was slight.

Case 4.—*History.*—A laborer aged 32, who came to the clinic for examination on June 24, 1934, had been well until two months previously, when a mild aching pain had appeared occasionally in the right supra-orbital, mandibular and aural regions. This had been attributed to an infected sinus and an unerupted wisdom tooth. For three weeks there had been dizziness and blurring of vision, especially in the left eye. Ten days previously numbness had appeared in the left arm and leg, and because of this he had consulted a physician, who had probed the sinus

and obtained pus. After this the numbness had disappeared. Two days previously he had worked as usual, but on his way home he had become somewhat confused. On the following morning he had attempted to get out of bed and had fallen to the floor. The left side had become paralyzed; he had been "groggy"; speech had been thick, and he had complained of headaches. During the day he had become more stuporous and had vomited occasionally, and the extremities occasionally had twitched. He entered the hospital at 8 a. m.

Examination.—The patient was drowsy but responded when called. The systolic blood pressure was 130 mm. of mercury, and the diastolic pressure, 50 mm. There were almost complete ptosis of the right eyelid and moderate ptosis of the left. The right pupil was dilated and immobile; the left pupil was small and responded poorly to light. The optic disks were slightly hazy. Elevation of the right eye was impossible and that of the left eye was greatly restricted. On the left side were: complete hemiplegia, slight increase in the tendon reflexes and absence of the abdominal reflexes and extensor responses of the toes with the Babinski and Chaddock methods. The patient passed into coma, and the neck became rigid. The pressure of the cerebrospinal fluid, while the patient was lying on his side, was 36 cm. of water. The cerebrospinal fluid was clear; Kolmer's modification of the Wassermann test gave a negative result. The protein content was 30 mg. per hundred cubic centimeters of fluid. The Nonne-Apelt reaction of the cerebrospinal fluid was negative. There were 10 small lymphocytes and 2 neutrophils in each cubic millimeter of the fluid, and the benzoin reaction was 000000333100000.

Course.—The patient grew rapidly worse and died fourteen hours after his admission to the hospital. A presumptive diagnosis of cerebral tumor, possibly accompanied by hemorrhage, was entered.

Autopsy.—Permission was obtained to examine the brain only. This organ was very soft, especially the right hemisphere, in the region of the insula and the occipital lobe. These structures were pale and semiliquid. There were marked thickening and almost complete obliteration of the right middle cerebral artery; yet the lumen did not contain a recent thrombus. The left middle cerebral artery was also thick and partially obstructed. The posterior cerebral artery on the right was occluded by a recent thrombus, but that on the left seemed normal. Both anterior cerebral arteries had thick walls, and their lumens were almost occluded. The basillar artery was normal, as were all arteries in the posterior fossa.

Microscopic examination of the brain tissue showed many regions in various stages of degeneration. In some degeneration was complete, and the entire region was full of scavenger cells which contained fat droplets. In other regions degeneration was well advanced and all the nerve cells had disappeared. There were swollen and disintegrating astrocytes, and many microglia cells were developing into scavenger cells. In other regions remnants of nerve cells were present and astrocytes showed early swelling, while the microglia cells were still not fully developed into scavenger cells. In still other foci were seen only edema, shrinking of the nerve cells, widening of the tissue spaces and proliferation of the microglia cells at the edges of the foci. In some places petechial hemorrhages had occurred in the cortex. Where the softening had extended into the white matter the myelin sheaths and axis-cylinders showed degeneration. In several foci we observed complete disappearance of nerve cells and a marked overgrowth of astrocytes, which formed a dense scar. These were considered to be foci of chronic infarction. The left hemisphere was better preserved than the right, and there were fewer foci

of degeneration and no gross infarction. The most remarkable changes were seen in the arteries arising from the carotid system and in the right posterior cerebral artery. The right internal carotid artery just proximal to its point of division into the anterior and the middle cerebral artery was the site of mild chronic periarteritis; there was slight thickening of the adventitia, which contained lymphocytes and a few plasma cells. Most of the media and the internal elastic lamina were normal, but the intima had proliferated so that the lumen was reduced to approximately one fourth of its normal size. One small segment of the media was necrotic and contained many polymorphonuclear leukocytes, which had penetrated into the proliferated intima.

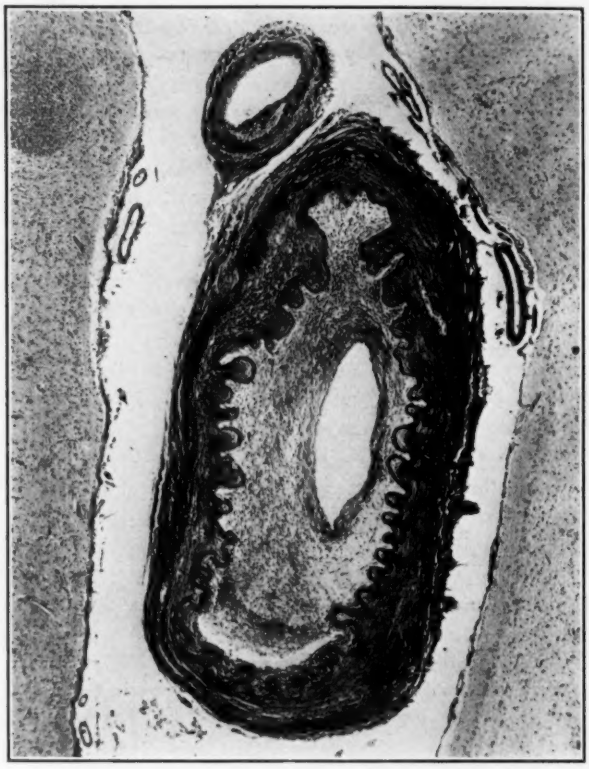

Fig. 6.—Right middle cerebral artery, showing almost healed periarteritis nodosa. The intima shows marked proliferation and reduction in the size of the lumen; the media has been almost completely replaced by fibrous tissue, and the adventitia is also proliferated. Van Gieson's stain; × 32.

Immediately distal to the origin of the right middle cerebral artery was an area of chronic periarteritis nodosa. There were many lymphocytes and plasma cells in the adventitia, which had proliferated and contained a large amount of well formed, adult connective tissue. The media was reduced in thickness and contained few smooth muscle fibers, but there was an excess of connective tissue which stained red with the Van Gieson method. The intima had proliferated to such an extent that the lumen of the vessel was reduced to less than a fifth of its normal size. This intimal proliferation was made up of connective tissue which stained faintly with the Van Gieson method (fig. 6). Weigert's elastic stain revealed

that the internal elastic lamina was excessively thick; there was little splitting of this layer, but a new layer of fine elastic tissue had grown around the newly formed lumen in the vessel and fine strands of elastic tissue had permeated the proliferated tissue, which partly filled the lumen of the vessel. The left middle cerebral artery, just distal to its origin, showed changes almost identical with those in the right, except that there were fewer lymphocytes in the adventitia and the inflammatory process had almost subsided. The connective tissue stained a deeper red with the Van Gieson method. Proliferation of the intima was more extensive, and the lumen was reduced to a tenth of its normal size. The increase

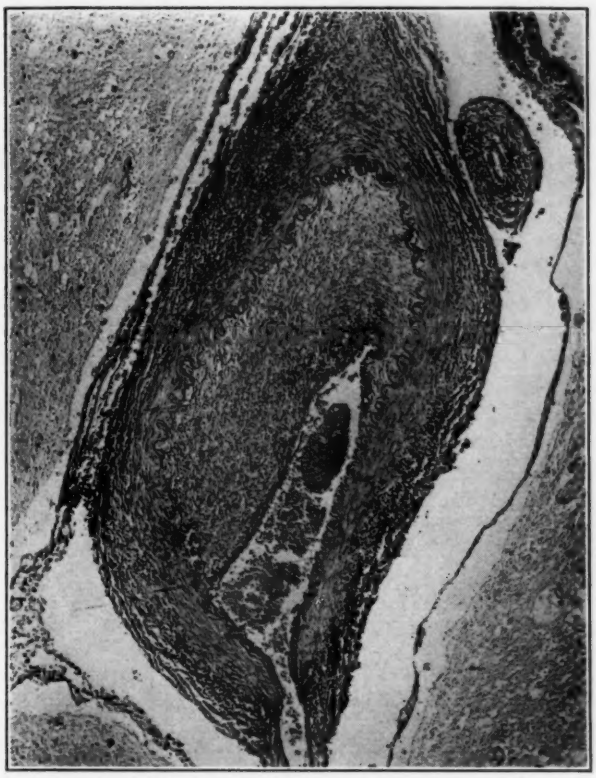

Fig. 7.—A slightly different level of the vessel illustrated in figure 4, showing more residual inflammation in the outer portion of the media and adventitia at one place. One may note the area of chronic periarteritis nodosa around a smaller artery. Hematoxylin and eosin stain; × 45.

in elastic tissue and the splitting of the internal elastic lamina were more marked in places on the left side than on the right. The small arteries close to the larger ones were in a state of chronic inflammation, and many lymphocytes and plasma cells were present in the adventitia (fig. 7). There was less proliferation of the connective tissue of the adventitia in the small than in the large vessels, and in some vessels the intima had not proliferated. However, in a few arteries the intima had proliferated until no lumen was visible. In both anterior cerebral arteries the arteritis had almost completely subsided, and only a few lymphocytes were present in the adventitia (fig. 8). Proliferation of the intima had reduced the

lumens to approximately a third of their normal diameter. About 1 inch (2.5 cm.) beyond the obstructions in the middle and anterior cerebral arteries the vessels were normal. However, in the subarachnoid spaces of the frontal and parietal lobes a few arterioles showed evidence of chronic periarteritis nodosa, and around these vessels were patches of local meningitis. However, most of the arteries were normal, and no meningitis surrounded them. The arteries and arterioles in the substance of the brain were normal except those in and near the foci of infarction, around which were lymphocytes and débris, the result of disintegration of tissue. The right posterior cerebral artery was occluded partly by the inflammatory process of periarteritis nodosa and partly by a partially organized thrombus. The

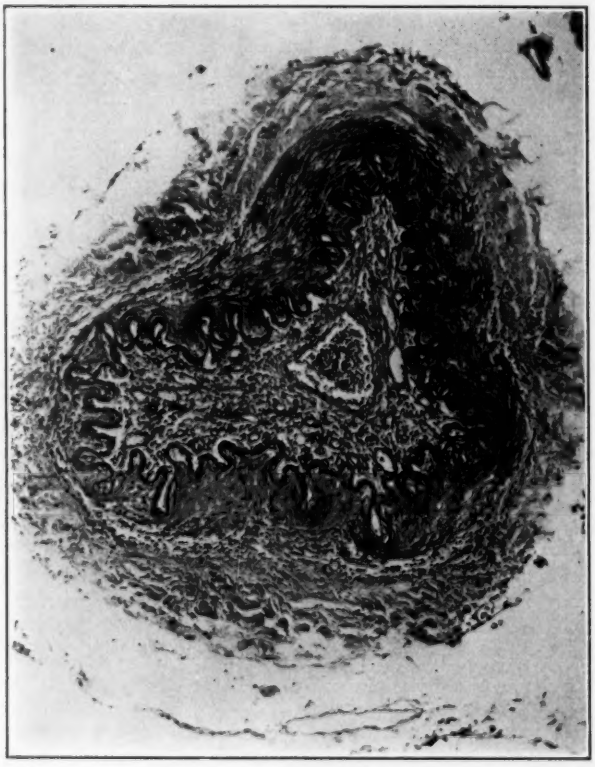

Fig. 8.—A small branch of the right middle cerebral artery, showing almost complete absence of the media on the left side and bulging of the internal lamina. This is almost an aneurysmal dilatation; the process is nearly healed, and the lumen has been much compromised. Weigert's elastic tissue stain; × 75.

inflammatory process was in the chronic stage of evolution. One and a half inches (3.7 cm.) distal to the area of periarteritis and thrombosis, the vessel was normal and the lumen contained erythrocytes.

The left posterior cerebral artery and all the arteries in the posterior fossa were normal. No lesion was observed in the arteries of the choroid plexus.

The periarteritis nodosa in the main branches arising from the internal carotid arteries was almost healed, but in some of the smaller branches it was in a chronic state of evolution. Proliferation of the

intima had progressed to a remarkable degree, so much so that it is difficult to understand how the brain obtained sufficient blood through these vessels. It was interesting that the arterial lesions, with one exception, were limited to the branches of the carotid system, while the arteries of the vertebrobasilar system were normal.

CASE 5.—*History.*—A physician aged 46 came to the clinic on May 15, 1936, because of fatigue, pain in the forearms and lower extremities, irregularity of the heart and polyuria. At the age of 6 years he had had diphtheria; at the age of 13, mumps and orchitis on the right side, and at the age of 19, gonococcic urethritis; tonsillectomy had been performed at the age of 25, and appendectomy, at the age of 30; at the age of 31 he had had an infection of the left thumb.

He had enjoyed good health until February 1936. About February 1 his automobile had been stalled, and he had become thoroughly chilled by exposure to a temperature of —24 F. Three or four days later he had felt chilly and for several days had had fever, severe backache in the lumbar region and pain in the calves and forearms. After he had spent three weeks at a sanatorium the pain disappeared, but at night he often became drenched with sweat and was disturbed three or four times to pass from 1,500 to 2,000 cc. of urine. After he had returned to work for two or three days, the exhaustion and pain had reappeared. Appetite had become poor, and within three months he had lost from 20 to 25 pounds (9 to 11.3 Kg.). For three weeks before his admission there had been intermittency in the action of the heart, and slight edema of the ankles, especially of the left, had appeared.

Examination.—The patient did not appear to be acutely ill, but was extremely weak. There was slight edema of the lower extremities. The weight was 195 pounds (88.5 Kg.); there was still moderate obesity. Systolic blood pressure was 166 mm. of mercury, and the diastolic pressure, 118 mm. The right testis was atrophied. The pulse rate was 76, and the temperature, 98.6 F. Vision was 6/7 with the right eye and 6/6 with the left; examination of the eyegrounds did not reveal any abnormality. Five or six times a minute there was an extrasystole. The urine was normal except for an occasional pus cell. The hemoglobin concentration was 15.4 Gm. per hundred cubic centimeters of blood; the erythrocytes numbered 4,050,000, and the leukocytes, 8,900 per cubic millimeter of blood. A differential blood count and examination of the blood smear showed nothing abnormal. Flocculation tests with the blood gave negative results for syphilis. Roentgenograms of the head, thorax, kidneys, ureters and bladder showed nothing abnormal. The urea content of the blood was 26 mg., and the sugar content, 109 mg. per hundred cubic centimeters. An electrocardiogram showed a rate of 83, premature contraction of the ventricles, slurring of the QRS interval in leads II and III, preponderance of the left ventricle, a notched P wave in lead II, a diaphasic P wave in lead III and an inverted T wave in lead III. No alarm was felt concerning the patient's condition when he was dismissed on May 17. He was advised to take additional rest.

Course.—The patient returned for examination on June 14, 1936. He was pale; there were slight puffiness of the eyelids, which he said was natural, and possibly slight cyanosis. Appetite had become poor, and each attempt to eat had been followed by vomiting. He lost another 20 pounds (9 Kg.). Exhaustion had increased, and pains in the extremities had "driven him wild." He added that about January 1935 he had tried to reduce and taken about 2 pounds (746 Gm.) of magnesium sulfate and some dinitrophenol, and that since February 1936 there

had been severe headaches once or twice weekly, as though the head were in a vise. He sometimes had fallen asleep while consulting, and a frostbite of the left foot acquired in February had left numbness along the lateral aspect of the foot. Since his previous visit to the clinic his temperature often had risen to 103 or 104 F., and the severe sweats had continued. He occasionally had become depressed and had cried. One week before he returned to the clinic he had awakened to find vision dim and the conjunctivae inflamed and edematous. Nocturia had increased, and he had had to void eight or ten times each night.

Vision with correction was 6/15 in the right eye and 6/10 in the left eye. The visual fields were roughly normal. The retinal arterioles were generally slightly narrowed; there were marked angiospasms in some of the smaller branches and diffuse angiospastic retinitis, characterized by edema of the optic disk and retina of both eyes and a few "cotton wool" patches and hemorrhages. There also were localized angiospastic lesions in the arteries of the choroid and extensive subretinal edema, which produced detachment of the lower peripheral portion of the retina of the right eye. Dr. H. P. Wagener made the notation that the lesions showed a striking resemblance to those seen in retinitis associated with the toxemia of pregnancy. The heart rate was 108 beats per minute. There was no apparent enlargement of the heart; the tones were tumultuous, and there was marked accentuation of the aortic second sound. Hourly readings of the blood pressure were taken on a number of occasions between June 18 and June 30; the systolic blood pressure varied from 150 to 210 mm. of mercury, with an average of about 180 mm.; diastolic pressure varied from 98 to 170 mm., with an average of about 110 mm. The pulse rate varied from 88 to 136 beats per minute. During the first week of the patient's stay in the hospital the temperature remained normal, but subsequently rose to a maximum of 104.4 F. The peripheral arteries were decidedly sclerotic. The capillaries of the nail folds in both limbs showed long loops and a decrease in caliber; there was a markedly increased spurting flow. There was generalized muscular tenderness, especially of the quadriceps, biceps and supraspinatus muscles.

On June 20 the arterioles of the retina appeared to be more vasospastic and irregular than they had been. The edema of the upper part of the retina had become less; there were more "cotton wool" patches in the retina of the left eye and a lobulated detachment of the lower part of the retina of the right eye. The upper margin of the detachment was 4 disk diameters below the disk, and the retina was elevated about 5 or 6 diopters. There was a well demarcated detachment of the lower part of the retina of the left eye, which was elevated about 4 diopters. By June 22 the liver, which had not been palpable, had descended about 9 cm. below the costal margin in the right mammary line, and the spleen was palpable. An attack of edema of the lungs, which was associated with bloody sputum and cyanosis, suggested acute cardiac failure; the patient recovered temporarily from this attack. Except for pronounced general weakness, muscular tenderness and some confusion, the results of neurologic examination were essentially normal. Respiration was sometimes rapid and deep and sometimes shallow. On June 23 spinal puncture showed the fluid to be under a pressure of 30 cm. of water when the patient was lying on his side. There was prompt response to jugular compression tests. The Nonne-Apelt reaction of the spinal fluid was positive. There were 4 lymphocytes per cubic millimeter and 50 mg. of protein per hundred cubic centimeters of fluid. There was no characteristic change in the electrocardiogram. In spite of a large output of urine and diminishing edema, there was marked renal insufficiency; the urea was 202 mg., and the creatinine, 8.8 mg. per hundred cubic centimeters of blood.

On June 27 the patient was semistuporous, but comfortable. There was occasional twitching of the muscles of the arms and jaw, and some part of the body was in constant motion. The appearance of the retina had not changed much; examination revealed marked angiospasm of some of the arteries, papilledema of about 2 diopters, with hemorrhages and exudates on the disks and "cotton wool" patches and exudates characteristic of residual edema around the macular region. The lobulated detachments of the retinas had increased in height to about 8 diopters. The pressure of the spinal fluid was 20 cm. of water, and responses to jugular compression tests were prompt. The Nonne-Apelt reaction of the spinal fluid was positive; there were 19 lymphocytes and 4 neutrophils in each cubic millimeter of the fluid, and the colloidal gold reaction was 0011210000.

On June 29 the patient passed into coma; the pupils were widely dilated, and there were jerking movements of various muscles. The tendon reflexes were present and equal on the two sides, and the Babinski sign was not elicited. Respiration of the Cheyne-Stokes type appeared. The systolic blood pressure was from 90 to 102 mm. of mercury, and the diastolic pressure, from 80 to 90 mm. The urine, which at first was normal, subsequently contained many erythrocytes and a moderate amount of albumin. The lowest value for the hemoglobin was 11.9 Gm. per hundred cubic centimeters of blood, and the least number of erythrocytes was 3,370,000 per cubic millimeter of blood. The greatest number of leukocytes was 25,100 per cubic millimeter of blood. On June 26 a differential blood count showed 8 per cent lymphocytes, 4.5 per cent monocytes, 86.5 per cent neutrophils, 1 per cent myelocytes and 1.5 per cent normoblasts. The percentage of eosinophils never exceeded 2.5. The presence of myelocytes in the blood smear was evidence of toxemia. Cultures of the blood and spinal fluid were sterile. The urea of the blood continued to increase, from 32 mg. to 390 mg. per hundred cubic centimeters. The highest value reached by the creatinine of the blood was 8.8 mg. On June 19 the value for the serum sulfates was 4.2 mg., which is a normal concentration. The value for the chlorides decreased to 445 mg. per hundred cubic centimeters of plasma. The carbon dioxide combining power of the plasma ranged from 53 to 70 volumes per cent. On June 19 the value for urea clearance was 58 cc., and that for sulfate clearance, 55 cc.; both these values are within normal limits. On June 22 cholesterol was 151 mg. per hundred cubic centimeters of plasma; calcium, 8 mg. per hundred cubic centimeters of serum; sodium, 313 mg. per hundred cubic centimeters of serum; nonprotein nitrogen, 67 mg. per hundred cubic centimeters of blood; protein, 5.6 Gm. per hundred cubic centimeters of serum, and the albumin-globulin ratio, 1 : 1.2. It is evident that between June 19 and June 29 marked renal insufficiency developed. On the latter date the urea content of the blood was 390 mg., and the creatinine content, 8.8 mg. per hundred cubic centimeters. These findings, together with the urinary and subsequent pathologic findings, indicate that between the two dates renal infarction had taken place.[19]

The patient died on the morning of June 30. The diagnosis was: acute arterial disease with hypertension; acute vasospastic crises, which were of eclamptic nature; acute retinitis with detachment of both retinas; myocardial degeneration with decompensation; acute dilatation of the heart; acute pulmonary edema; chronic passive congestion of the liver and spleen; renal insufficiency, and uremia.

Necropsy.—There were evidences of diffuse arterial disease. The heart was hypertrophied; the kidneys were atrophic and had many old and recent infarcts, and many small hemorrhages were visible in the fundus of each eye. There was no gross evidence of arteritis or aneurysmal formations. We regret that we did

19. Rosenberg, E. F.; Wagener, H. P., and Keith, N. M.: Unpublished data.

not obtain portions of any peripheral nerves for microscopic examination. Gross changes were not present in the brain.

Microscopic examination of the various organs of the body showed diffuse periarteritis nodosa, in the chronic stage of evolution. In a few places we observed acute arteritis and hyaline necrosis of the inner portion of the media, but in most of the small arteries there was chronic periarteritis, which was associated with proliferation of the intima and almost complete obstruction of the lumens.

There was chronic periarteritis around several of the smaller meningeal arteries in the depths of some of the sulci of the brain. There was little proliferation of the intima of most of these arteries, although it was prominent in a few. We did not find any, even small, acute or chronic infarcts in the brain. The cerebral arteries were normal except for slight thickening of the media, which was the result of hypertension. The most interesting microscopic changes in this case were those in the arterioles of the choroid of the eye. The arterioles of the retina showed thickening of the media, which was the result of hypertension. In approximately 20 per cent of the arterioles of the choroid there existed hyaline-like necrosis of the media. This tissue was fragmented and clumped into small masses and simulated the changes in amyloid disease (fig. 9). It stained bright pink with eosin and did not contain any nuclei. No inflammatory reaction had yet occurred in the media. There was no proliferation of the intima, and although all the arteries in which necrosis of the media had occurred were widely dilated and irregular in outline, we could not be certain that aneurysms were beginning to form. Choroidal arterioles normally have little adventitia, but around the arterioles in which necrosis of the media had occurred we observed slight proliferation of adventitial connective tissue. As a rule there was no periarteritis, but around one or two arterioles we observed small collections of lymphocytes. However, there were no polymorphonuclear leukocytes or foreign body giant cells.

The most interesting feature of this case was the early evidence of periarteritis nodosa in the arterioles of the choroid. Descriptions of such changes in the choroid are rare. It also was interesting that most of the other evidences of periarteritis nodosa in the body indicated chronic or almost healed arteritis. However, one of the main characteristics of the disease process, at least in our experience, is the presence of lesions in various stages of evolution. In all probability, the periarteritis nodosa was the cause of the detachment of the retina in both eyes.

COMMENT

It is easy to understand the modus operandi of periarteritis nodosa if the disease process is separated into two phases. The first, or fundamental, phase is the lesion involving the small arteries of various organs or parts of the body, and the second phase includes the effects of the diseased blood vessels on the tissues which they supply. We have used throughout the reports of the cases in this study the term "periarteritis nodosa" because it is the one most commonly in use, but it is in reality a misnomer. The primary lesion in the arteries is hyaline-like necrosis of a portion of the media and the internal elastic lamina. This is followed by extension of the inflammatory process

to the adventitia and by periarteritis. The perivascular inflammation is thus secondary to the lesion in the media of the artery. While the periarteritis is developing there is usually proliferation of the intima, which produces narrowing of the lumen of the vessel; it is to this narrowing that the secondary changes in the various organs or tissues are due. It is during the subacute stage of the inflammatory process that aneurysms of the arteries are thought to develop, but in all our cases gross aneurysms had failed to form. This is a common observa-

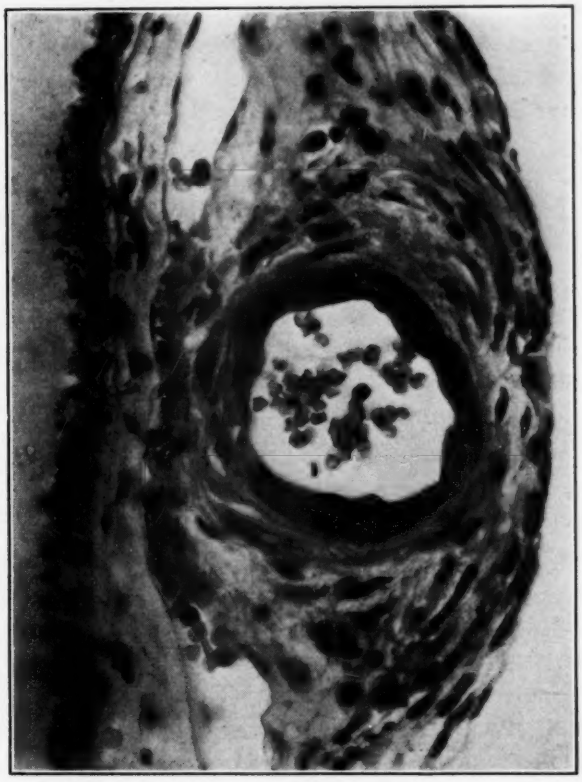

Fig. 9.—Arteriole of the choroid. There is hyaline necrosis of the internal elastic lamina and inner half of the media; the process is so early that no inflammatory reaction has as yet appeared; the outline of the lumen of the vessel is irregular; there is an early, but slight, proliferation of the adventitia, but none of the intima. Hematoxylin and eosin stain; × 435.

tion in the recorded cases. In other words, the "nodosa" feature is the exception, not the rule. The general conception of periarteritis nodosa is that the medium-sized vessels are involved in the inflammatory process, but in our experience it is the much smaller arteries, almost the prearterioles, which are involved. The largest vessels involved in any of our cases were those in case 4, in which the middle cerebral

vessels were affected. Thromboses only rarely form in the narrowed lumen of the arteries, but occasionally such a lesion has been described in which recanalization had occurred. It is characteristic of periarteritis nodosa that all vessels are not included in the inflammatory process and that not the walls of the entire vessel which is involved but only segments, and frequently only short segments, are diseased. It is thus necessary to cut many sections from different levels; otherwise, the diseased portion may be overlooked. The occluded portion of the artery is usually proximal to the degeneration of the nerve, and microscopic sections obtained at the level of the most severe lesions in the artery show normal, or almost normal, nerve tissue, while sections obtained below this level show markedly degenerated nerves and normal appearing arteries. Contrary to the usual teaching, we observed that the arterial lesion ended abruptly.

Curtis and Coffey [20] said that it was surprising that the number of instances of hypertension was not greater in a disease which produces so great a vascular resistance. In three of our cases hypertension was pronounced. In these cases the vascular lesions were widespread, while in the other two cases involvement of the arteries was limited; we think that the hypertension depends on the extent of the arterial bed involved in the obstructive process. In case 1 the arterial disease was limited to the nutrient arteries of the nerves, and we think that this involvement was not sufficient to raise the blood pressure. In cases 2, 3 and 5 the arterial disease was widespread and could account for the hypertension. On the other hand, it is possible that there was coexisting hypertension independent of the periarteritis nodosa. It was interesting that the hypertension had produced hypertrophy of the media of the small arteries and arterioles not included in the inflammatory process.

In several of the cases which we have studied we observed arteritis in more than one stage of evolution. This was more often the rule than the exception and is a satisfactory explanation of the exacerbations and remissions to which patients suffering from periarteritis nodosa are subject. We did not observe any arteries in which we considered that the disease had reached the healed stage, although in some it was almost healed and there were only a few lymphocytes in the periadventitial fibrous tissue. In these arteries the media had been almost completely replaced by adult connective tissue, and the internal elastic lamina had reformed and was even hypertrophied. The elastic tissue usually invaded and extended throughout the intimal proliferation and formed a layer beneath the endothelial cells of the new lumen. This formation of new elastic tissue was a late manifestation of the disease. In the

20. Curtis, A. C., and Coffey, R. M.: Periarteritis Nodosa: A Brief Review of the Literature and a Report of One Case, Ann. Int. Med. **7**:1345-1358, 1934.

acute stage of the disease the necrosis of the inner portion of the media involves the internal elastic lamina, which becomes fragmented and often disappears; however, new elastic tissue grows as healing advances. In many cases reported in the literature eosinophilia was a prominent feature, but in our cases it was almost negligible. We are unable to observe any excess of eosinophils in sections of the lesions in the arteries. We have no evidence, except in case 1, which suggests that periarteritis nodosa has any affinity for nerve tissue; yet a review of the literature shows that clinical neuritis is one of the most common, and frequently an early, symptom of the disease. It has been claimed that about 20 per cent of patients suffering from periarteritis nodosa have symptoms referable to the peripheral nerves, but our impression is that neuritis is much more common. Pathologists seldom remove portions of peripheral nerves for routine study, and even in cases of neuritis nerves are not always removed for microscopic study. In the present study we neglected to remove portions of peripheral nerves for examination in case 5, in spite of the fact that pains in the legs were an early and persistent symptom. The chief interest in this case was centered in the diffuse vascular disease, which overshadowed in clinical importance the neurologic manifestations of the disease.

We believe that the lesions in the nerves are solely the result of inadequate blood supply. We saw many infarcts in the nerves which we examined; in some nerve bundles there was only one infarct (fig. 2); in others there were several, and in still others the infarcts had become confluent. At lower levels in the nerves the regions of infarction became disseminated throughout the numerous nerve bundles, and in this way the lesions seemed to be chronic and diffuse. Occasionally, a large region of infarction, which was the result of occlusion, or partial occlusion, of a large artery, involved several nerve bundles. The normal ramification of the nerve bundles with each other leads to dissemination of the degenerated nerve tissue into all the bundles. The occluded vessel was at a higher level than the infarct, so that the actual source of the infarct was not always immediately obvious. There was no inflammation in any of the nerve bundles, so we were not dealing with neuritis in the sense of inflammation, but there always was edema, even above the level of degeneration. We feel assured that the infarcts were the cause of the degeneration and of the clinical manifestations of pain and weakness from which most of these patients suffer. There was a marked increase in the number of cells of the sheath of Schwann in the nerve bundles which had undergone the most marked degeneration. The nerve roots between the spinal cord and the dorsal root ganglia were normal, as were the dorsal root ganglia themselves. We did not find any evidence of periarteritis nodosa in the skeletal muscles in any of the cases. Involvement of the central nervous system occurs

in about 8 per cent of cases of periarteritis nodosa. In case 4, it was interesting to note that the lesions in the larger arteries were almost healed while in the smaller arteries the lesions were subacute; in the latter proliferation of the intima was slight, while in the former it was profound. It was proliferation of the intima of the larger vessels which produced the inadequate blood supply to the brain and, thus, the symptoms and the death of the patient. Another interesting observation was the absence of arteritis in all but one of the branches of the vertebral arteries, while the lumens of all the branches arising from the internal carotid arteries were severely compromised. There was no evidence of periarteritis nodosa in the arteries in the brain. In case 5 there was no inflammatory lesion in the arteries in the substance of the brain, but some periarteritis in the vessels in the subarachnoid space. In this case early necrotizing arteritis was present in the media of the arterioles of the choroid. This is a rare complication. The similarity of lesions involving the vessels of the choroid and the meninges, on the one hand, and those involving the vessels of the retina and the substance of the brain, on the other, has been recognized previously by Keith, Wagener and Kernohan,[21] in a study of arteriolar changes associated with malignant hypertension. The association of vascular changes in the choroid of the eye and in the meninges was present in the case reported by Goldstein and Wexler.[18] In none of our cases were the veins involved in the inflammatory process, and the sympathetic nervous system escaped direct injury, except that in one case several small branches arising from the semilunar ganglion were the sites of infarction.

SUMMARY

We have presented the clinical histories in five cases of periarteritis nodosa in which microscopic changes were observed in the nervous system. In three cases the peripheral nervous system was widely degenerated; in one the brain, and in one the choroid of the eye, was involved. In one case only the nutrient arteries to the peripheral nerves were involved in the inflammatory process. The degeneration of the peripheral nerves appears to be the result of occlusion or marked narrowing of the lumens of the nutrient arteries to the nerves. The degeneration, which is diffuse at lower levels, begins as infarction at higher levels. The infarcts may be single, multiple or confluent, and at times an infarct may involve several nerve bundles. There was no inflammation in any of the nerves. We observed periarteritis nodosa at different stages of evolution, even in the same case. This probably explains the exacerbations and remissions which occur in this disease.

21. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141-188 (Feb.) 1928.

DISCUSSION

DR. HARRY LEE PARKER, Dublin, Irish Free State: As a discusser of this paper, I had the privilege of reading it before it was presented. The thing that impressed me most was the meticulous care with which each case was investigated, both from the clinical and from the pathologic side. I believe that Dr. Kernohan and Dr. Woltman have tried to make a difficult subject easy.

Probably every one thinks that periarteritis is a rare condition; at least I believe that it is. I remember seeing but one patient who I thought might be suffering from it. On the other hand, many diseases have in the past been thought to be rare until pioneers in the field, like Dr. Kernohan and Dr. Woltman, have shown that the condition exists and can be recognized.

The patient I have in mind was a woman about 45. No definite diagnosis of her condition was made. It was only after reading Dr. Woltman's paper that it struck me that I had been dealing with a case of possible periarteritis nodosa. In brief, neuritis of the femoral nerve developed, which produced wasting of the quadriceps extensor muscle. For no particular reason, improvement appeared after three or four months, but atrophy of the muscle persisted. Later on, neuritis developed in the left leg, with numbness, paresthesia, loss of reflexes and a certain amount of pain, to be followed by numbness and tingling in the left hand, suggesting peripheral neuritis. The confusing fact was that the so-called neuritis did not present the symmetrical distribution characteristic of multiple neuritis and had the mysterious habit of appearing and disappearing.

This seems to be characteristic of periarteritis nodosa. It has its periods of exacerbation and its intervals of remission. The unfortunate element in the disease, however, is that it may involve any portion of the nervous system—brain, spinal cord or peripheral nerves. It may simulate syphilis or any other disease, and in any given case I, frankly, should have considerable difficulty in making a clinical diagnosis because of its bizarre, complex and polymorphic picture.

I should like to ask Dr. Woltman and Dr. Kernohan their opinion as to the method or methods by which a definite diagnosis of this condition can be made. It occurs to me that in any case in which periarteritis nodosa may be suspected it is advisable to take a specimen for biopsy from a peripheral nerve, muscle or artery. If, on the other hand, as I understand, the disease travels from artery to artery, the particular artery subjected to biopsy might be one not involved. I should like to ask, therefore, if there is any short cut by which a clinician like myself can make a diagnosis and be sure of it.

DR. G. W. HOWLAND, Toronto, Canada: I wish to answer that question from experience gained in a case of definite periarteritis nodosa in the wards of the Toronto General Hospital. This patient complained of abdominal pain, marked loss of weight, sciatica and brachial neuritis, the last clearing up rapidly. Eosinophilia was present, with a count of as high as 40 per cent of the polymorphonuclear cells. A series of six or seven purpuric spots appeared in the left lumbar region, and the following day a swelling was observed in that region, which contained a palpable vessel; this was removed for biopsy. The pathologic report on this specimen showed all the characteristics of periarteritis nodosa. The patient shows marked clinical variations between improvement and relapse.

DR. LLOYD H. ZIEGLER, Albany, N. Y.: I wish to report briefly my experience with two patients, on both of whom autopsy was performed. One patient showed the characteristic lesions in the blood vessels on the surface of the heart chiefly, and, so far as I know, had no neurologic manifestations of the disease. The other was a woman in the forties with distressing pain in the legs, the examination of

whose blood revealed tremendous eosinophilia. She had convulsions, lost weight and became extremely emaciated, despite many therapeutic efforts. She had visual hallucinations in the right field of vision which she described as "small babies floating up through the air." She was not confused, but laughed and wept easily. She died after a severe convulsion, and autopsy revealed fairly old multiple infarcts of the organs of the body, including the left calcarine region. The pathologic lesions of the arteries were characteristic throughout the body, but were not demonstrated in the brain. It was suspected that the infarct was the result either of an embolus or of the periarteritis nodosa. The brain is being studied carefully, and the case probably will be reported here.

DR. ISRAEL STRAUSS, New York: This is a disease not infrequently diagnosed in a general hospital, but not proved by autopsy in many instances. Occasionally it is diagnosed and proved by autopsy or biopsy. It is interesting that in all cases reported no one has yet found an etiologic factor. No organism has been isolated which has been proved to be the basis of the disease. Furthermore, the disorder, interestingly, is not uncommon in children. It is not only the adult who suffers from it. Strangely, too, the disease, having many manifestations, may avoid the nervous system altogether. Occasionally, as pointed out by the authors of the paper, the nervous system is extensively involved. Such a patient came into my service. Strangely, the first sign of his illness appeared after a rhinologist had punctured a sinus for relief of nausea and headache. After the puncture there was edema of the face. From that time he began to show symptoms involving particularly the cranial nerves, such as bilateral deafness, paralysis of the tongue and blindness. My colleagues and I were puzzled as to the cause of the condition, the blood cultures all being sterile. The sinuses showed mild involvement. Hematuria then developed; immediately becoming suspicious, we asked Dr. Edwin Beer, who was in charge of the genito-urinary service, to investigate the cause of the hematuria. Although he found nothing, he suggested that the condition might be periarteritis nodosa, and the diagnosis was verified.

It is interesting that the histories of many of these patients, especially children, reveal involvement of the upper respiratory tract, even asthma, but the relationship of that involvement to the disease no one has thus far been able to point out, unless it is allergic.

DR. JAMES W. KERNOHAN: In some cases reported in the past the clinical diagnosis has been made because the clinician or neurologist suspected the nature of the disease process and established the diagnosis by biopsy. In most cases, however, the diagnosis has been made only at necropsy.

I agree with Dr. Strauss that this disease is not nearly as rare as it is at present supposed to be. A study of the literature reveals that about 8 per cent of patients with periarteritis nodosa have neurologic manifestations. I think that the percentage is really much higher.

In most of our cases, particularly the last, there was definite hematuria, and involvement of the kidneys was much more marked than implication of other organs. Involvement of the nervous system was the least marked of all.

Another disconcerting question is the one which Dr. Parker mentioned, namely, where one should take the specimen for biopsy. That is a problem which I cannot solve, because longitudinal sections through an affected vessel may show normal structure for a considerable distance, then, abruptly, a small nodule extending for 3 or 4 mm. and then a normal vessel beyond that point, with a tapering off thrombotic process. I believe that it is a matter of luck, to a certain extent at least, as to finding the region where one should take the biopsy specimen, except that any lesion in the skin or tender spot in the muscles is probably the best place from which to take the specimen.

THE NUCLEUS LATERALIS MEDULLAE

AN EXPERIMENTAL STUDY OF ITS ANATOMIC CONNECTIONS IN MACACUS RHESUS

GEORGE A. BLAKESLEE, M.D.

ISRAEL S. FREIMAN, M.D.

AND

S. E. BARRERA, M.D.

NEW YORK

In the lateral region of the medulla, between the inferior olive and the descending trigeminal root, lies a fairly large group of cells about which considerable confusion exists. This nucleus has been described under various names, including the nucleus funiculi lateralis, nucleus reticularis lateralis and nucleus lateralis medullae. Most observers agree that this nucleus is a part of the afferent system of the cerebellum. Impelled by studies on the cerebellum and its connections initiated by Ferraro and one of us (S. E. B.), we undertook to study this nucleus carefully and to define as precisely as possible its architecture and its afferent and efferent connections.

The location, structure and connections of this nucleus of the medulla have been discussed by Tilney and Riley,[1] Strong,[2] Cajal,[3] Jacobsohn,[4] Marburg,[5] Brun,[6] Ranson,[7] Weed,[8] Ariëns Kappers,

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Read at the Sixty-Third Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 4, 1937.

From the Neurological Department of the New York Post-Graduate Medical School and Hospital, Columbia University College of Physicians and Surgeons, and the Department of Neuropathology, the New York State Psychiatric Institute and Hospital.

1. Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, ed. 2, New York, Paul B. Hoeber, 1923.

2. Strong, O., in Bailey, F. R.: A Text-Book of Histology, ed. 7, William Wood & Company, 1925.

3. Ramón y Cajal, S.: Histologie du système nerveux de l'homme et des vertébrés, Paris, A. Maloine, 1909, vol. 1, p. 934.

4. Jacobsohn, L.: Ueber die Kerne des menschlichen Hirnstammes, Neurol. Centralbl. **28**:674, 1909.

5. Marburg, O.: Die Anatomie des Kleinhirns, Deutsche Ztschr. f. Nervenh. **81**:8, 1924.

6. Brun, R.: Zur Kenntnis der Bildungsfehler des Kleinhirns, Schweiz. Arch. f. Neurol. u. Psychiat. **1**:61, 1917; **2**:48, 1918.

(Footnotes continued on next page)

Huber and Crosby [9] and others. A careful perusal of this literature, however, has convinced us that there is considerable disagreement among the various observers as to the nomenclature, architecture and connections of this group of cells.

PRESENT OBSERVATIONS

Fifteen Macacus rhesus monkeys, each averaging 10 pounds (4.5 Kg.), have been used so far in our studies. The brains of several monkeys of this group were studied in serial section with the Nissl stain to determine the architecture of the nucleus. Our observations agree fairly closely with those of Cajal.[3] As may be seen in figures 1, 2, 3 and 4, the nucleus lies in the lateral white column of the medulla, between the formatio reticularis and the surface and between the inferior olive and the descending trigeminal root. Low in the medulla there is no difficulty in distinguishing these cells from those of the formatio reticularis, which are analogous to the large motor cells of the ventral horn of the cord. The nucleus first appears just above the lowest level of the pyramidal decussation, and from that region runs cephalad as a continuous column of cells. Increasing rapidly in size, its broadest development is achieved at the inferior pole of the olive. Its upper pole is situated with some variability at or below the midolivary plane. The nucleus forms a compact, well delineated structure in its lower portion; the upper part, however, becomes irregular, and its form varies from monkey to monkey. However, two main cell groups are to be discerned—a large, ventral group, lying on the dorsal surface of the olive, and a small, dorsolateral group, which reaches to the descending trigeminal root (figs. 2 and 3). At times, in a few sections, a small group of cells is seen detached from this group and lying beneath the trigeminal root. This corresponds to the linear nucleus of Cajal and the subtrigeminal nucleus of Jacobsohn. There are several cell types. The majority are fairly large, stellate, multipolar cells, which are observed in the lower segments of the nucleus and in the ventral group in higher segments. Medium-sized, more ovoid cells are seen in the dorsolateral group and only in upper segments (fig. 4). In the subtrigeminal group one observes large, elongated, fusiform cells. At the higher levels cells

7. Ranson, S. W.: The Anatomy of the Nervous System, ed. 5, Philadelphia, W. B. Saunders Company, 1935.

8. Weed, L. H.: A Reconstruction of the Nuclear Masses of the Lower Portion of the Human Brain Stem, Publication 191, Carnegie Institution of Washington, 1914.

9. Ariëns Kappers, C. U.; Huber, A. C., and Crosby, Elizabeth: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936.

are seen which resemble more closely those of the reticular formation, but these are few.

Several monkeys were studied after complete ablation of the cerebellum and after section of the inferior cerebellar peduncle. After several months the brain stem was studied in serial sections with the

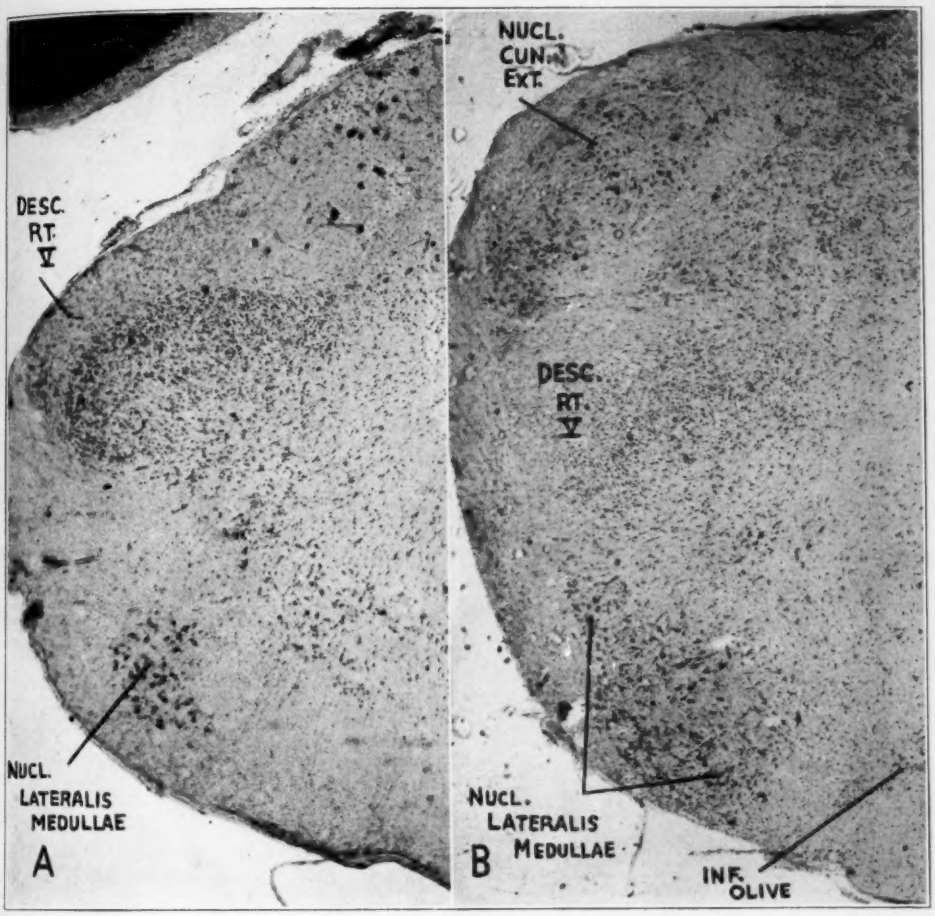

Fig. 1.—Medulla of Macacus rhesus (Nissl stain). *A* is from the level of the pyramidal decussation, and *B*, from that of the inferior pole of the inferior olive. In this figure and in the accompanying figures, *DESC. RT. V* indicates the descending root of the trigeminal nerve, and *NUCL. CUN. EXT.*, the external cuneate nucleus (nucleus of Clarke and Monakow).

Nissl stain. The results of the two sets of lesions were the same. All the cells of the nucleus lateralis were observed to have disappeared (fig. 5), except for the few reticular cells noted before at higher levels.

This confirms the observations of Van Gehuchten [10] and Yagita.[11] It indicates that all efferent connections are with the cerebellum, by way of the restiform body. It also tends to vitiate the statement of Jamieson [12] that "some fila of the spinal root of the accessory nerve and of the motor nerve of the first cervical arise from the nucleus lateralis."

Transverse lesions were made in the lateral region of the upper cervical region of the cord. After two weeks the brain and cord were

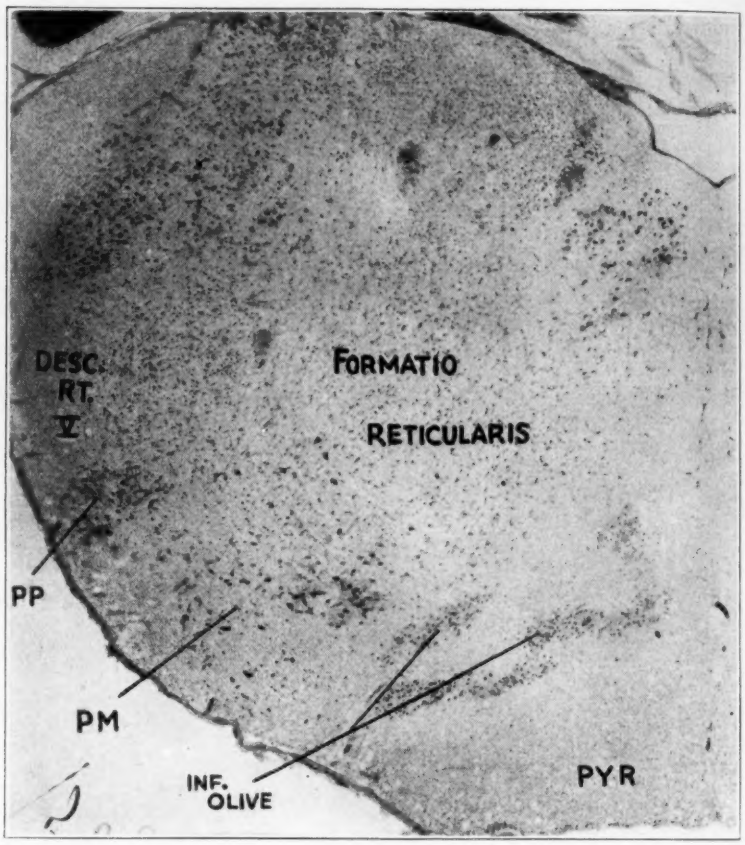

Fig. 2.—Level of the lower third of the inferior olive in Macacus rhesus. Note the pars magnocellularis (*PM*) and the pars parvocellularis (*PP*).

10. Van Gehuchten, A.: Le corps restiforme, Névraxe **6**:135, 1904.

11. Yagita, cited by Schäfer, E. A.; Symington, J., and Bryce, T. H.: Quain's Elements of Anatomy, ed. 11, London, Longmans, Green & Co., 1908, vol. 3, pt. 1, p. 127.

12. Jamieson, E. B.: Companion to Manuals of Practical Anatomy, ed. 2, Baltimore, William Wood & Company, 1925, p. 327.

stained by the Marchi method. Serial sections of the cord and medulla were studied in an effort to trace ascending fibers to the nucleus lateralis. In several monkeys with discrete lesions of the dorsal spinocerebellar tract, degenerated fibers could be traced to the dorsal region of the nucleus (figs. 6, 7 and 8). These fibers seemed in the main to be of smaller diameter than those of the tract itself, and in all probability were mainly collateral fibers. In animals in which the ventral spinocerebellar tract could be traced as a distinct bundle, it was noted that the ascending degenerated fibers were in contact with the nucleus and

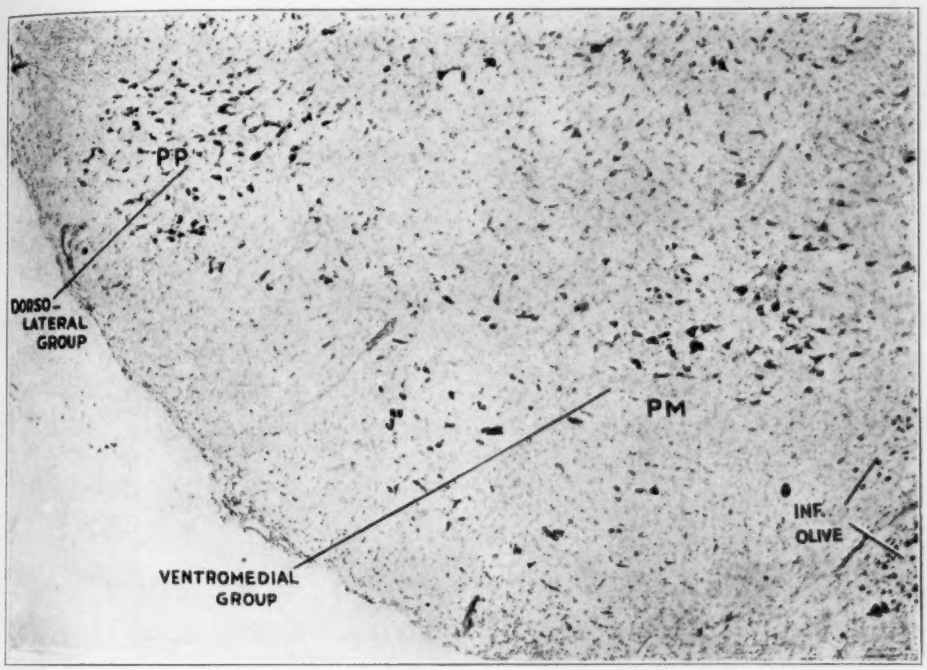

Fig. 3.—A higher magnification of the section shown in figure 2. Note the size of cells in the ventromedial and dorsolateral groups as compared with that of cells in the inferior olive.

that numerous fibers ascended through the outer part of the nucleus (figs. 8, 9 and 10). In a number of sections collateral fibers could be seen to disappear within the body of the nucleus. These connections were more distinct than those of the dorsal tract.

In one monkey a distinct and complete lesion of the lateral column of the cord was produced at the fourth cervical level. In addition to the spinocerebellar and spinothalamic tracts at the periphery, a large number of ascending fibers were seen scattered diffusely through the

lateral column at higher levels (figs. 6, 7, 8, 9 and 10). When the nucleus appeared, it developed in the midst of these fibers (fig. 7). At higher levels the nucleus was surrounded by these fibers, but, in addition, many of the fibers were intimately mingled within the body of the nucleus. These external and internal fibers frequently seemed to end in (i. e., to disappear within), and to give off collateral fibers to,

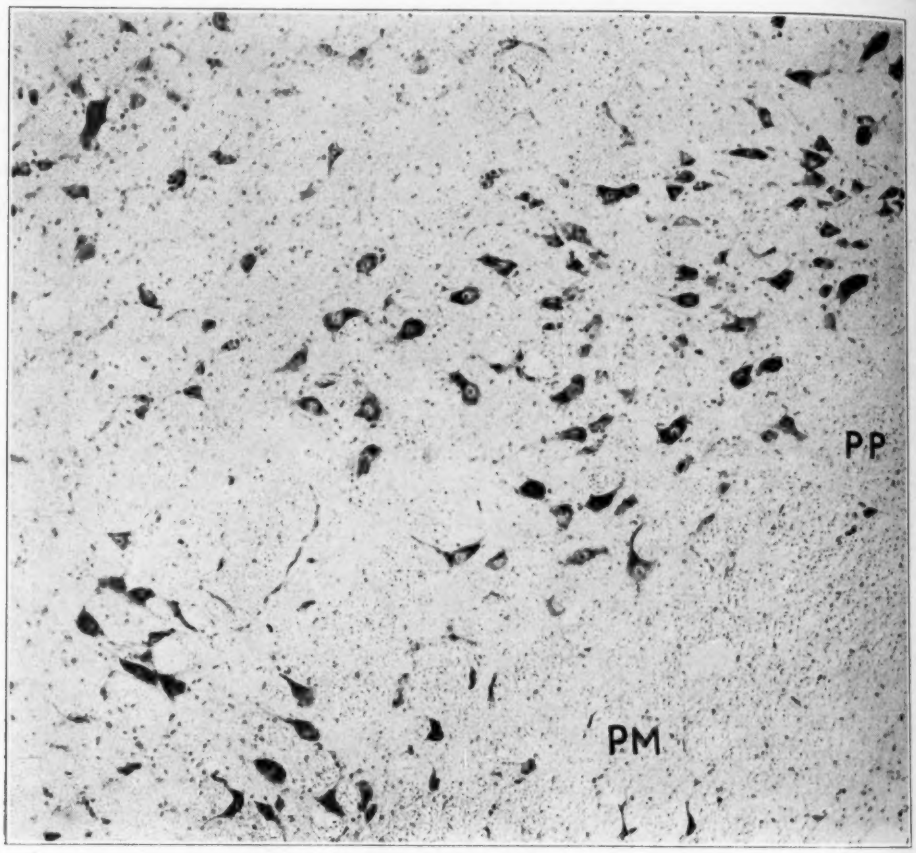

Fig. 4.—Region of the lower third of the olive (× 140), showing the nucleus lateralis medullae. Note the large cells of the pars magnocellularis (*P M*) and the medium-sized cells of the pars parvocellularis (*PP*).

the nucleus. At still higher levels these fibers made their way dorsolaterally about the nucleus lateralis, to appear for a time as a distinct bundle under the descending trigeminal root. In a few sections the subtrigeminal nucleus could be seen lying within this bundle of fibers, completely surrounded by, and apparently receiving fibers from, them.

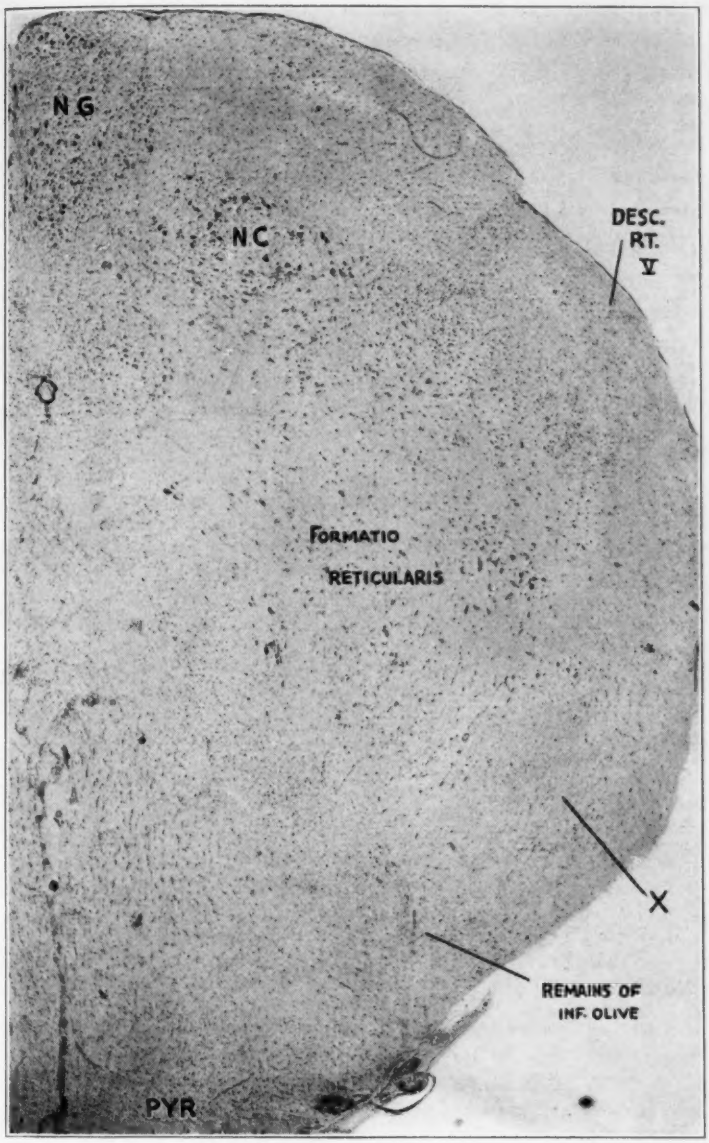

Fig. 5.—Level of the inferior pole of the inferior olive in an acerebellar monkey, showing the nucleus gracilis (*NG*) and the nucleus cuneatus (*NC*). Note the absence of cells in the region of the nucleus lateralis medullae (*X*).

After the dorsal spinocerebellar tract had entered the restiform body, the group of fibers from the lateral column proceeded to run through and around the descending trigeminal root to enter the restiform body. None of these fibers could be traced to higher levels. This observation confirms those of Cajal regarding the relation of this nucleus to the

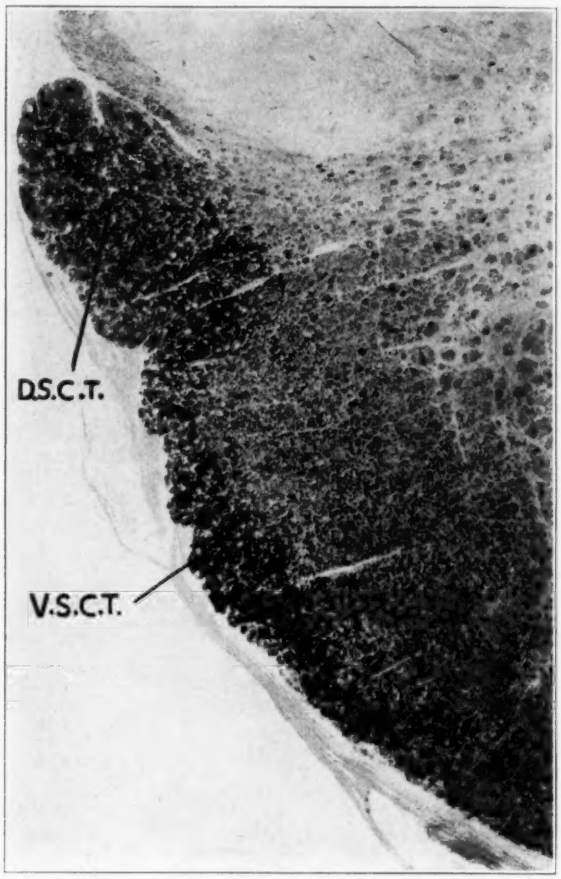

Fig. 6.—Section of the medulla of the monkey at the beginning of the pyramidal decussation, after unilateral lesion of the lateral column at the fourth cervical segment. Note the degenerated fibers scattered throughout the lateral column. *D.S.C.T.* indicates the dorsal spinocerebellar tract, and *V.S.C.T.*, the ventral spinocerebellar tract.

lateral column, but it seems to rule out, at least as far as the monkey is concerned, any connection of the lateral column with structures at higher levels than that of the nucleus lateralis. The fibers which Van

Gehuchten described as reticulocerebellar and the presence of which Papez [13] reported after lesions of the reticular formation dorsal to the inferior olive may be only the ascending fibers of the lateral column of the cord on their way to the cerebellum.

In a monkey with a lesion of the nuclei of the dorsal column on one side, the internal arcuate fibers could be clearly followed. In pass-

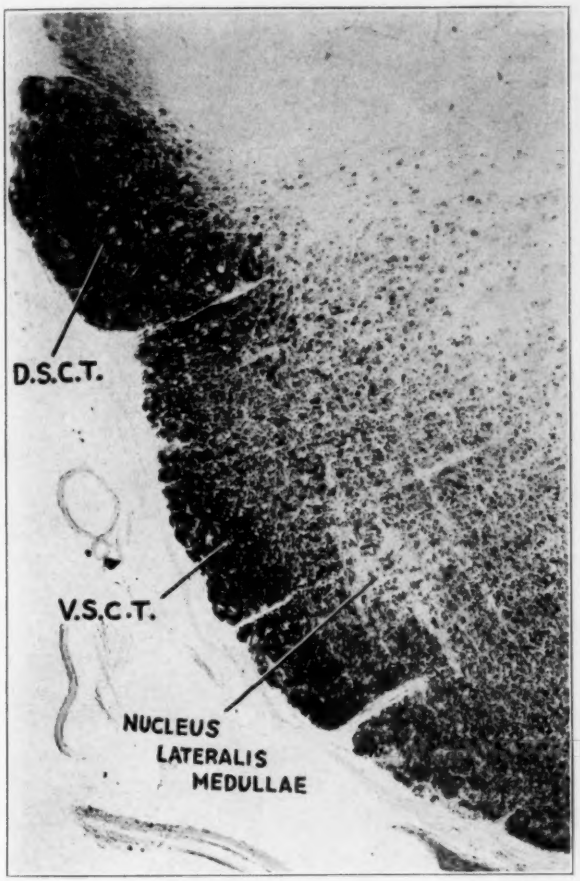

Fig. 7.—Section of the medulla of the monkey through the beginning of the nucleus lateralis medullae, within the ascending fibers of the lateral column.

ing to the opposite medial lemniscus, a number of these fibers could be traced between the contralateral inferior olive and the pyramid, as

13. Papez, J. W.: Reticulo-Spinal Tracts in the Cat, J. Comp. Neurol. **41**:365, 1926.

noted by Ferraro and one of us (S. E. B.),[14] and around the olive laterally. In a few sections these fibers seemed to reach the ventral portion of the nucleus lateralis, but no distinct connections with it, such as Marburg described, could be ascertained. In all probability, the fibers which make contact with the nucleus ascend to join the medial lemniscus at higher levels. It may be that the fibers which Marburg described

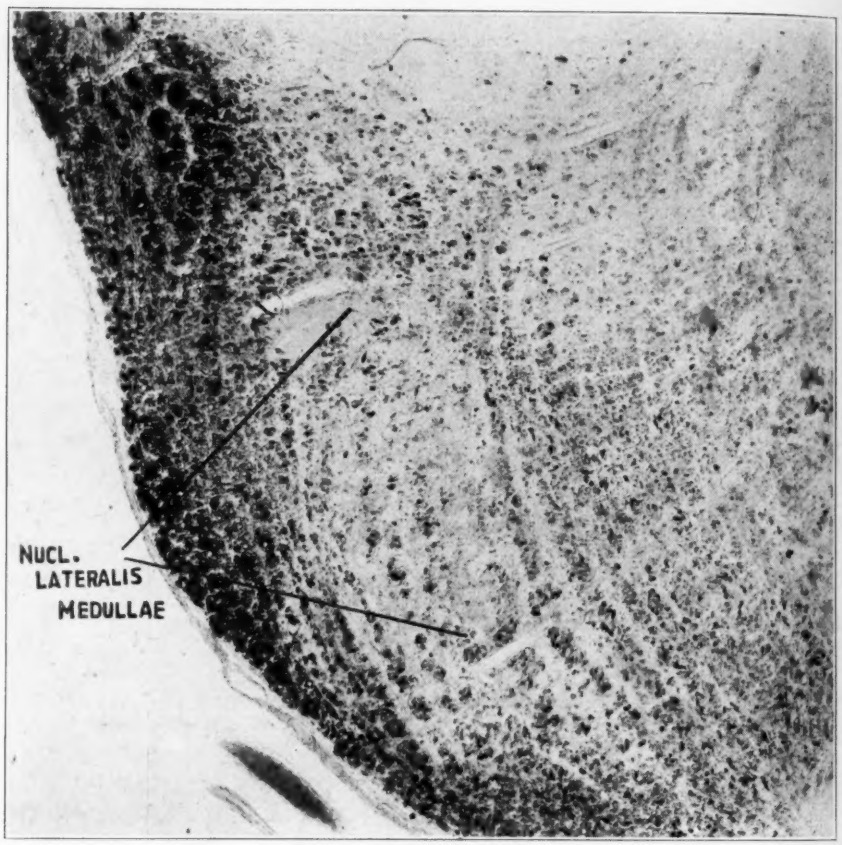

Fig. 8.—Level of the inferior pole of the inferior olive in the monkey. Note the degenerated fibers surrounding the nucleus and numerous collaterals within the nucleus.

as reaching the nucleus lateralis from the nuclei of the contralateral dorsal column by passing between the olive and the pyramid or through the latter, are the external arcuate fibers which Papez described as arising from the reticular nucleus of the raphe and cells in the ventral

14. Ferraro, A., and Barrera, S. E.: Unpublished data.

portion of the medulla at this level. In a number of sections degenerated fibers were traced from the damaged nuclei of the dorsal column as they crossed the internal arcuate fibers and ran laterally through the reticular formation to reach the dorsal group of the nucleus lateralis of the same side.

In several monkeys an attempt was made to obtain a direct lesion of the nucleus. None of these was successful. The lesions were

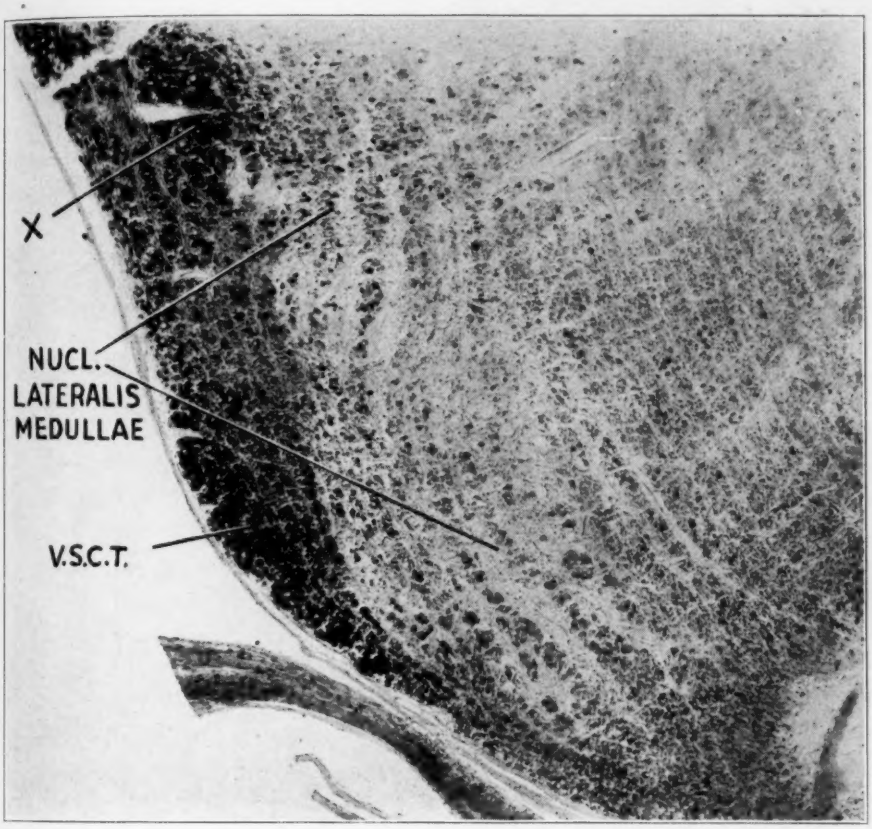

Fig. 9.—Section at a level slightly higher than that shown in figure 8. Note the concentration of the ascending fibers of the lateral column under the descending root of the trigeminal nerve, at *X*. The dorsal spinocerebellar tract has already passed into the corpus restiforme.

observed to be situated in the reticular formation, between the inferior olive and the descending trigeminal root, rostral to the nucleus. In these cases descending fibers could be traced which belonged to the rubrospinal and vestibulospinal tracts and, presumably, also to the central tegmental pathways. As the rubrospinal tract descends, it is inti-

mately related to the dorsal group of cells; some of its degenerated fibers could be seen running through the nucleus. However, no definite connections with it could be established. In some of the sections it was possible that there were connections between the nucleus and the reticular formation.

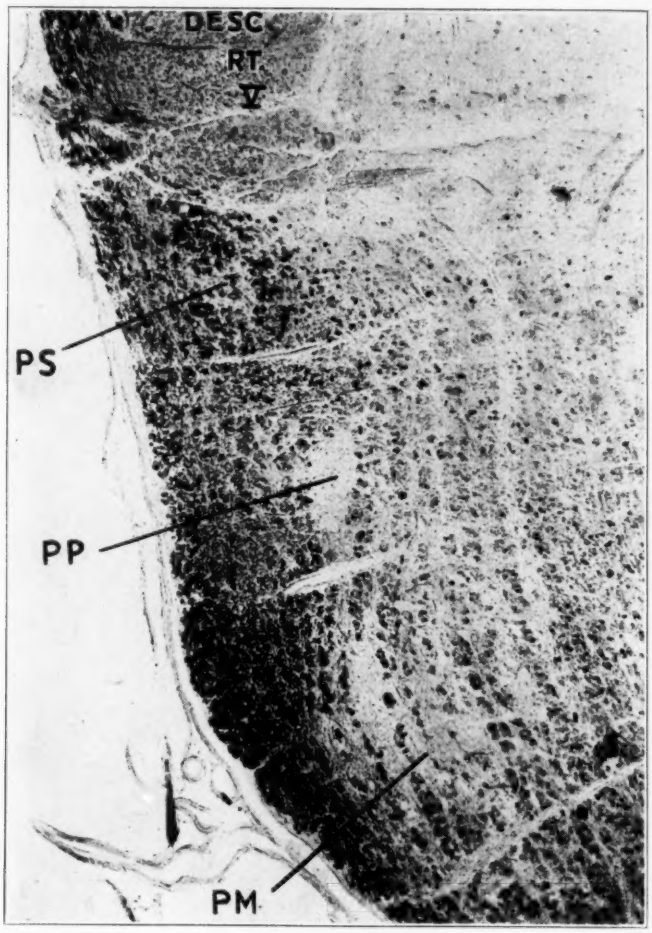

Fig. 10.—Section at a still slightly higher level than that shown in figure 9. Note the appearance of the pars subtrigeminalis (*PS*) within the group of fibers seen in figure 9.

SUMMARY

As regards the structure and form of the nucleus lateralis, our observations on Macacus rhesus agree fully with those of Cajal on lower mammals. They disagree with the observations of Weed on man as to the extent of the nucleus. We find the nucleus consistently to

exist in the lower as well as in the upper segments of the medulla, whereas Weed reported it to be present only at upper levels. The nucleus contains a pars magnocellularis, a pars parvocellularis and a pars subtrigeminalis. In addition to receiving fibers from the ascending pathways of the lateral column of the cord, however, afferent connections were, in all probability, established with the dorsal and ventral spinocerebellar tracts. In addition, a small proportion of afferent fibers were traced from the nuclei of the homolateral dorsal column. No distinct connections were established with higher levels. All the efferent fibers of the three cell groups were believed to enter the cerebellum by way of the homolateral restiform body. Hence, the three groups constitute a single system.

Our studies point to the nucleus as a relay between ascending pathways of the cord and the cerebellum. Its afferent stimuli are probably all proprioceptive. Its relays are not with the lateral column alone. Hence, the designation nucleus funiculi lateralis is misleading and true only in part, and the term should be discarded. Nor is there any reason for calling it a reticular nucleus. In view of the multiple sources of its afferent connections, it seems best to retain the name nucleus lateralis medullae as least confusing. The nucleus forms part of a relay system which includes the arcuate nucleus and the nucleus of Clarke and Monakow, and these transmit presumably proprioceptive stimuli from the spinal cord to the cerebellum.

CONCLUSIONS

1. The nucleus lateralis medullae was studied in Macacus rhesus.

2. Its morphologic relations were established. It extends through a large part of the medulla.

3. Afferent connections were established with the lateral column of the cord, the dorsal and ventral spinocerebellar tracts and the nuclei of the homolateral dorsal column.

4. The efferent pathway of the nucleus is entirely to the cerebellum, via the restiform body.

5. The nucleus lateralis constitutes, with the arcuate nucleus and the nucleus of Clarke and Monakow, a relay system between ascending proprioceptive pathways of the cord and the cerebellum.

6. The designation nucleus lateralis medullae seems most appropriate and least confusing, and should be retained.

7. Aside from the spinocerebellar tracts in the periphery of the cord, a large number of ascending fibers lie scattered diffusely through the lateral column of the cord which ultimately enter the restiform body, and presumably reach the cerebellum.

DISCUSSION

Dr. Louis Hausman, New York: Sherrington described the cerebellum as the chief proprioceptive ganglion of the central nervous system, implying that this organ receives certain deep afferent impulses from various parts of the body. The first question to be answered, then, is whether the lateral reticular nucleus falls into the scheme of things.

It is known that the cerebellum receives impulses from the segments of the spinal cord through the ventral and dorsal spinocerebellar systems and through fibers from the accessory cuneate nucleus (described by von Monakow and Blumenau). It is also known that these systems convey to the cerebellum special information from the skeletal muscles which serves as an indicator of activity for these segments. Does a similar arrangement exist for the caudal segment of the hindbrain? In this segment of the brain stem, activity of the skeletal muscles is represented by the hypoglossal and the ventral nucleus of the vagus nerve. It is generally accepted that the cerebellum is functionally connected with the corresponding skeletal muscles of this group; if this is so, one must ask: How do the pertinent afferent impulses reach the cerebellum? Does the lateral reticular nucleus, which appears so conspicuously in the caudal segment of the hindbrain, immediately ventral to the descending root of the trigeminal nerve, serve this purpose, much as Clarke's column serves the muscles of the trunk?

Others have suggested that the lateral reticular nucleus may be part of the arcuate system. If so, one should expect this nucleus to be connected with the corticopontile system, for the arcuate nuclei are really part of the pontile nuclei. However, the authors have found no such evidence, as a result of their experimental sections through the midbrain, indicating any descending connections with the nucleus.

Attempts have also been made by some investigators to relate the lateral reticular nucleus to the inferior olivary nuclei, but the evidence has been insufficient and unconvincing.

It is more logical to think that this nucleus is related to the reticular gray matter of the caudal segment of the hindbrain, and it would be well, therefore, to determine whether it receives deep afferent impulses from the skeletal muscles connected with this segment. It would be difficult to understand its function if it served merely as a relay station in the spinocerebellar system.

Dr. Blakeslee and his co-workers are to be commended for calling attention again to the cells of this diffuse reticular gray nucleus, which occupies so large an area of the brain stem but still remains uncharted and obscure. I hope they will continue investigations along these lines.

Dr. S. E. Barrera: In the absence of Dr. Ferraro, may I take the liberty of saying a few words? This study has been concerned with the connections of the nucleus which reach it from regions situated further caudad and with whether the fibers of the spinocerebellar system and of the lateral column end in the nucleus or pass through it to reach higher structures. This distinction is always difficult when methods such as the Marchi technic are used. However, sections were made in several planes in an attempt to elucidate this problem, and a study of horizontal as well as frontal sections has tended to convince us that some of the fibers in the ventral spinocerebellar tract and lateral column actually end in the nucleus.

With regard to the efferent pathways: We know that the nucleus completely disappears not only after removal of the whole cerebellum but with section of the unilateral restiform body at a level just before it passes ventral to the eighth nerve. This indicates that the fibers pass into the restiform body. We are now

attempting to study serial sections in Nissl preparations of monkey brains with sharply localized lesions of various portions of the cerebellum, to ascertain where the fibers from the lateral reticular nucleus end in the cerebellum.

Another interesting feature is the possibility of making direct lesions in the nucleus. This is fraught with great difficulties. Many fibers pass through the region surrounding this nucleus; included among these are fibers ascending from the cord and fibers from the opposite olivary nucleus which cross and enter the restiform body. Therefore, any lesion made from the ventrolateral aspect of the medulla will surely cut some of these fibers, particularly those from the opposite olive, as well as those from the ventral spinocerebellar tract and lateral column. For this reason, combination experiments are being made with preliminary destruction of the olivocerebellar fibers, either by a direct lesion of the contralateral olive or by a midline section of the olivocerebellar fibers. A preliminary section of the spinal cord on one side will eliminate the fibers ascending from the cord. After complete degeneration of these fibers, we are attempting to make direct lesions in the nucleus, with the idea of studying the resulting degenerations by the Marchi method.

EXPERIENCES WITH INSULIN SHOCK THERAPY IN SCHIZOPHRENIA

HANS H. REESE, M.D.
MADISON, WIS.
AND
ADRIAN VANDER VEER, M.D.
CHICAGO

Despite the extent of the literature on therapeutic research in schizophrenia, the psychosis has been essentially unmodifiable by external means. As long as the underlying pathobiologic processes are not known treatment can be only empirical; perhaps through actually discovered correlations the starting point for an effective therapeusis may be achieved, as in the case of dementia paralytica and pernicious anemia.

Sakel's treatment differs from all previous therapeutic attempts in that its goal is the daily production in each patient of profound hypoglycemic coma. America has been rather tardy in investigating the new treatment, although during the last year articles have begun to appear and insulin shock therapy has been started in many places. It must be stated at the outset that this procedure is not to be played with. Though fatalities are rare, the patient is always in a more or less precarious state during deep hypoglycemia. Moreover, the response on any one day is not definitely predictable from the previous course, and the patient's condition may change at any moment. Constant medical supervision by a well informed clinician is, therefore, an indispensable necessity, and the treatment should be given only in a specially organized unit of a hospital.

The histopathologic changes in insulin intoxication have been thoroughly studied in man and animals. In cases of fatal insulin shock in diabetic patients, there have been observed: friability and dryness of the brain, glial proliferation, Nissl degeneration of the large ganglion cells and perivascular hemorrhages. These changes are similar to those in cardiovascular or circulatory psychoses and illustrate what happens when insulin coma is prolonged to fatal extremes. With a technic similar to ours, however, Schmid [1] observed that the only definite change in rabbits was hyperemia of the pial vessels. Similar reversible changes

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From the Wisconsin Psychiatric Institute, Madison, Wis., and the Mendota State Hospital, Mendota, Wis.

1. Schmid, H.: Zur Histopathologie der Sakelschen Hypoglykämiebehandlung der Schizophrenie, Schweiz. med. Wchnschr. **66**:960-961 (Oct. 3) 1936.

in the central nervous system, as the anatomic correlates of the alteration in cellular activities produced by insulin, must be assumed to exist in patients receiving treatment.

Prior to our investigation, we studied the literature as to possible alterations in the laboratory findings. These may be summarized as follows: There are practically no changes in the erythrocyte count or the hemoglobin concentration during shock; during the first hour there is usually mild leukopenia, which thereafter changes to moderate leukocytosis (with a count of about 15,000). This so-called sympathicotonic blood picture depends probably on the compensatory endogenous liberation of epinephrine. The sedimentation rate remains the same. The blood chlorides show slight diminution. The blood cholesterol varies inconstantly. The calcium and potassium levels in the blood change slightly, but not enough to be of importance. The blood phosphorus drops considerably—by about 25 per cent—and does not regain its resting value for twenty-four hours. The pulse rate is sometimes increased after insulin medication, but in other cases one observes definite bradycardia. The systolic pressure rises from 10 to 15 mm., with a corresponding drop in the diastolic pressure. We have found the sugar level of venous blood during coma to be between 14 and 40 mg. per hundred cubic centimeters; the average values are below 25 mg., and not infrequently below 20 mg. The higher values reported from Europe have apparently been found for capillary blood. The sugar content of the spinal fluid is likewise low, usually from 5 to 10 mg. higher than that of the blood; on one occasion, however, we found the value for sugar in the spinal fluid to be 17 mg., and that for the blood, 19 mg.

The cardiovascular findings are important because of the fact that insulin is said to constrict the coronary arteries, to which action have been attributed the deaths of several diabetic patients with coronary sclerosis. The electrocardiographic studies at Vienna and in Switzerland revealed only flattening of the T wave in leads III and IV, with occasional depression or reversal of the ST segment (fig. 1). These changes appear soon after the injection of insulin, but cease within a few hours after the termination of shock.

A word must be said as to the selection of patients. All persons are not suitable for this treatment, and subjects must be selected according to the duration of the illness. Once the psychosis is fixed or marked deterioration has occurred, improvement may be secured but seldom. It is while the process is still in flux that remissions may be achieved; in general, the more recent the onset the better the results. Sakel and his co-workers have had little success with conditions of more than six months' standing, while the Swiss investigators expressed the belief

that eighteen months marks the practical limit for therapeutic endeavors. Coronary disease is an absolute contraindication to treatment, as are severe pulmonary or cardiac disorders. We do not take patients over 40 years of age.

METHOD

After trying several variations in administration of insulin, we have adopted an altered form of Sakel's regimen, more like that of the Swiss investigators.

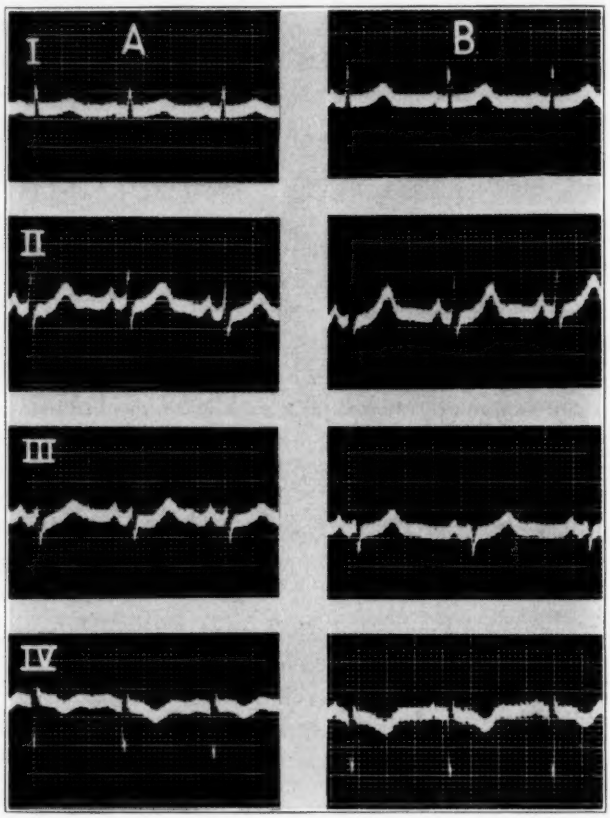


Fig. 1.—Typical findings in the electrocardiogram during and after insulin coma. The patient received 50 units of insulin at 6:45 a. m. The first electrocardiogram (*A*) was taken at 10:15 a. m., during moderately deep coma (blood sugar, 22 mg. per hundred cubic centimeters). The second electrocardiogram (*B*) was taken at 11:40 a. m., ten minutes after intravenous termination, with the patient awake.

The only significant change during coma is in the T wave, which is of less amplitude in all four leads than after termination. Similar changes have occurred in all the cases we have studied.

After the findings for the blood and urine have been checked for several days and the sugar tolerance and reactivity to insulin are established for the patient selected, he is ready for therapy. We now submit our patients on the first day to 60 units

of insulin, given intramuscularly at 7 a. m., with the stomach empty. From 8 a. m. until termination of coma, the patient must be carefully observed. By increasing the dose by from 10 to 20 units daily, according to the individual patient's symptomatic reactions, we obtain deep comatose hypoglycemic shock with from 70 to 220 units of insulin. Shock then is produced once each week day until it becomes apparent that no further progress is made. We consider that a therapeutic trial requires a minimum of two months. Thirty-one patients have been treated up to the present, with both good results and complete failures. One patient has received treatment since the middle of December 1936; a total of thirteen injections of protamine zinc insulin and fifty injections of plain insulin have been given; only after this long period is he beginning to show definite improvement with insight.

Once the shock dose of insulin has been determined for any patient, the amount usually is adhered to for some time; changes, however, are required from time to time by variations in the patient's reactivity. Moreover, during the course of treatment sensitivity to insulin usually manifests itself, requiring frequent reduction in the shock dose. In one case, for example, it was possible to reduce the insulin gradually from 160 to 30 units, deep shock being produced with both doses; in another case the reduction was from 80 to 25 units. The effective doses used so far have varied from 20 to 220 units in different cases at different stages of the treatment.

TYPES OF SHOCK

As the dose of insulin is increased, greater degrees of hypoglycemia are produced, and the patient falls into progressively deeper phases of insulin shock. In a typical case the course is as follows: With small doses of insulin, the response may be limited to light sweating and hunger. With large doses hunger is seldom complained of, its appearance being forestalled perhaps by the onset of coma. On the second, third and fourth days of treatment, the patient often does not react as much as he did on the first day, despite the greater dose. After this, however, the extent of the reaction generally parallels the amount of insulin given.

In common with other workers, we have noted three types of shock: wet, dry and convulsive. The first is the most desirable and the commonest type of reaction.

The sequence of events in ordinary wet shock is constant and typical, and recapitulates briefly the response of the patient during the first few days of treatment. Within an hour after the injection of insulin the subject sweats lightly and may feel hungry. This usually comprises his entire reaction on the first day of treatment. The next stage of shock is characterized by somnolence, slurred speech, ataxia, confusion, diplopia and often euphoria. This marks the extent of the patient's usual response on the fourth and fifth days. In a slightly deeper stage of shock there may appear some degree of purposeless psychomotor activity, which occasionally reaches a stage of wild excitement. This phase of agitation gradually subsides as the patient sinks into the coma

which characterizes the deepest stage of shock. As treatment is continued over several weeks, the hyperactivity tends to disappear and the whole course of shock is more quiet.

In early insulin coma, pathologic reflexes, such as the Babinski and Oppenheim signs, appear, rarely to be replaced by complete areflexia and atonia in the deepest stage of shock. In ideal deep wet shock, the subject is quiet and relaxed, sweats profusely in large drops and often drools saliva by the ounce.

Coma does not necessarily run a smooth course, however, but the depth may vary somewhat from one moment to the next. The patient may move about or open his eyes, but is never in contact with the environment. Sometimes a definite decerebrate posture appears, with rotation of the head, extension of the legs and of the sincipital (facial) arm and flexion of the occipital arm. The fingers may assume a tetanoid position, or the thumb may be folded tightly into the palm. On several occasions we have elicited unilateral tonic neck reflexes. Lesser degrees of decerebration appear more often in the form of tonic extensor spasms of all extremities, accompanied by hyperpnea and tachycardia, and often by cyanosis. Infrequently, partial asphyxia due to accumulation of saliva in the pharynx seems to be responsible, and the spasms cease with removal of the saliva; at other times, cessation is spontaneous and the patient falls into quiet coma; sometimes the spasms increase in severity until the shock has to be terminated. We have found the pulse in ideal deep shock to be full and generally slow. One of our patients regularly had bradycardia, with a rate of 38, even in mild hypoglycemia. The temperature likewise falls in wet shock to low figures, and care must be taken to avoid chilling.

Rarely, the patient falls into coma with little or no sweating. We then speak of dry shock. Sakel expressed the belief that this reaction indicates an unfavorable prognosis. We have noticed its variable appearance on a number of occasions, but only with one patient was it a regular occurrence. This subject regularly passed into dry coma at about 10 a. m. and into convulsions almost immediately. It was impossible to find a dose of insulin that would produce coma without convulsions. In an attempt to convert this reaction into wet shock, we used pilocarpine hydrochloride in doses of from 1/10 to 1/5 grain (from 0.006 to 0.012 Gm.) from one to two hours after the insulin was given. This produced profuse diaphoresis and prolonged the preconvulsive period of coma for about an hour, but a convulsion always occurred if shock was allowed to continue. The patient, who was in hebephrenic pseudostupor, eventually recovered, with full insight. We recommend further investigation into the use of pilocarpine or other parasympathetic drugs.

The last type of shock to be mentioned is the convulsive or epileptiform seizure. A convulsion may appear during hypoglycemia at any time, with or without warning, especially when high doses of insulin are used repeatedly. We have not yet encountered one which appeared without previous signs of hypoglycemia, though Sakel stated that this may occur. The usual convulsion is limited to generalized clonic movements with cyanosis. Such episodes, if mild, should be allowed to continue for a time, as they may terminate spontaneously. Intervention with intravenous administration of dextrose, however, is often advisable. Severe epileptiform seizures are rare; they demand immediate termination of the shock. A convulsion is by no means of bad prognostic import in our experience. One of our successfully treated patients experienced seventeen severe myoclonic convulsive episodes before recovering. A day or two of rest is advisable after an epileptiform fit.

A phenomenon said to occur late in the course of insulin treatment, on which Sakel laid great stress, is the so-called activated psychosis. This consists of the appearance of pronounced psychotic reactions during hypoglycemia in patients who are otherwise clear throughout the day. This condition represents the reverse of the situation at the start of treatment, when the only clear intervals appear during the shock and the patient is psychotic for the remainder of the day. Sakel has expressed the belief that this phenomenon is the last flare-up of the psychosis and continues treatment until its extinction.

Doubt has been cast on the validity of this concept by some writers, one of whom is Wilson, and it has been suggested that the activated psychosis represents merely fragments of an induced insulin psychosis, as seen in the syndrome of hyperinsulinism. While we have not observed activated psychotic phenomena in every one of our cases, they have been so striking in several instances as to leave no doubt of the correctness of Sakel's conclusion. We may summarize our experiences thus:

The early weeks of insulin shock therapy are usually stormy, with a variegated symptomatology, some of which has been described. The first lucid intervals always appear, however, in immediate relation to hypoglycemia, either in the precomatose phase or just after termination of coma. Moreover, patients who have hallucinations almost never report them as occurring in shock, probably because of the partial amnesia which exists for the hypoglycemic period.

As treatment continues and symptoms vanish, a period of comparative quiet ensues, when the patient's daily behavior shows only minor abnormalities and shock is relatively calm throughout. When activated psychotic phenomena appear, they disturb this picture markedly. Thus, one of our patients who was near the end of a course of treatments, possessed of insight and without abnormality in her daily behavior or in

shock, one day suddenly became wildly excited after intravenous termination. She tore off her garments, swore, fought with the attendants and required restraint to prevent possible self-injury. After eating she calmed down, apologized for her behavior and had insight for the episode. This excitement appeared on several successive days. Questioning revealed that a profound psychic upheaval was taking place in these intervals, with vivid hallucinations. Another patient complained that just after termination she had been horrified by the thought that her little boy was to be fed through the nasal tube. Immediately after eating she realized the delusional nature of this idea. A third patient described his experiences one day after two months of treatment, in these words:

"I had lots of goofy ideas today in insulin. They were crazy—just ideas. I thought everybody was vomiting [one patient had actually been sick] and that they were going to make me eat it. I thought they were going to make me go to hell. I fought a long time. I felt I had to get out of my nightshirt and take off the restraint sheet or be lost. It seemed as though I had made wrong judgments in the past and would be damned unless I could untie the restraints. As soon as I drank the sugar water, the ideas cleared up."

We do not yet know the prognostic significance of such manifestations. All we can say is that they appear only late in treatment. We continue therapy until they are no longer present.

TERMINATION OF SHOCK

We usually allow uncomplicated deep comatose wet shock to continue for from two to three hours, provided the total period of hypoglycemia has not exceeded six hours. There is no reason for prolonging coma beyond this limit; there is certainly danger of producing actual damage to the nervous system, and perhaps to the sugar-regulating mechanism.

Not infrequently, of course, complications ensue which require earlier termination. Some indications are: weak or irregular pulse; tachycardia, with a rate of over 150; respiration of the Cheyne-Stokes type; severe choreiform and athetoid jactitations; prolonged extensor spasms; hyperpnea; excessive salivation (and aspiration); cyanosis; sympathetic shock; pallor; spasm of the glottis; hunger or thirst excitement, and convulsions.

European workers have described four methods of interrupting hypoglycemia, three of which we have found satisfactory. If the patient can swallow (which he can still do automatically in the lighter degrees of coma, even when he is no longer clearly conscious), he may be given

two glasses of heavily sugared water, tea or eggnog (90 Gm. of sucrose to the glass). As soon as full consciousness returns a meal rich in carbohydrate is given.

If the patient is in deep coma, he may be brought to full consciousness in from one to five minutes by the intravenous injection of a 50 per cent solution of dextrose; from 10 to 30 cc. suffices. This is the method of choice when quick interruption is necessary. It has the disadvantage of causing gradual venous thrombosis when employed daily, unless the dextrose is followed by physiologic solution of sodium chloride. When this method is used, additional carbohydrate must, of course, be given by mouth, as the amount of dextrose injected will neutralize completely less than 12 units of insulin; if more carbohydrate is not given, the patient may fall into coma again later. It is always desirable to save one good vein, for conditions demanding quick interruption may arise with startling suddenness. If no peripheral veins are available we use the external jugular vein in emergency.

A third method of termination is the administration of a solution of sugar through the nasal tube. This is the procedure employed in Europe as a routine, and we have used it more and more of late. There are certain advantages, as well as disadvantages, in the nasal route. The method is simple and cheap, and the veins are saved for emergencies. The patients waken smoothly and gradually and can eat in from one half to three quarters of an hour. The disadvantages are: production of vomiting or spasm of the glottis (also mentioned by Sakel) and stimulation of excessive hyperpnea. We have noted the last difficulty on several occasions. As soon as the tube was passed the patient became extremely hyperpneic, and sucked in so much air through the tube with the diaphragm as to lend doubt as to its correct placement.

A final method of terminating shock is the intramuscular injection of from 1 to 2 cc. of a 1:1,000 solution of epinephrine. This procedure is recommended especially for the termination of epileptiform shock. We have not found it satisfactory, even when we used the intravenous route. Our experience with ephedrine has been similar. The patient can be roused from a light, but not from a deep coma, and convulsions, if present, are not visibly curtailed. Administration of epinephrine after a nasal feeding, however, shortens the time of recovery, and in cases of difficult arousal the intravenous administration of epinephrine may be of service.

In recovery from coma the subject exhibits the same symptoms as when entering shock, but in the reverse order. The higher functions, especially speech, are the last to reassert themselves, and the patient may exhibit motor aphasia for from fifteen to twenty minutes after he is otherwise fully conscious.

DIFFICULTIES AND DANGERS

Insulin therapy has been criticized, in particular by Berze,[2] on the ground that it subjects the patient to unwarranted dangers. Aside from the fact that severe, and even heroic, measures are justified by so malignant a disorder as schizophrenia (if they offer promise of relief), a consideration of the mortality figures reported from Europe and those obtained from our own experience tends, in our estimation, to minimize the importance of such accusations. Küppers [3] has recently summarized the available figures thus: Among 395 patients treated in four European series, there were only 6 deaths—a gross mortality of about 1.5 per cent. Even these few deaths were not all attributable directly to insulin, however, as a detailed consideration of the Vienna material shows.[4]

One hundred and sixty patients were treated in several sanitariums. Three patients died. The first fatality occurred when the treatment was being developed; insufficient carbohydrate was given after hypoglycemia, and the patient died of after-shock. The second death was attributable to coronary sclerosis with acute thrombosis, as revealed at autopsy; in the third instance, the patient went into convulsions as she was rousing from shock and died forty-eight hours later of acute hemorrhagic pancreatitis. Thus, of the 3 deaths, the first was caused by preventable negligence, and the second, by an undiagnosed physical disease, whereas only the third was possibly attributable to the insulin treatment per se.

That one may now anticipate a mortality of less than 1 per cent in a large series in which contraindications to treatment have been carefully observed is shown by the more recent Swiss statistics,[5] according to which only 1 of 118 patients died. Moreover, Schmid [1] has demonstrated by animal experimentation that a comparable technic produces only mild reversible changes in the central nervous system, which are practically limited to meningeal hyperemia. These facts speak eloquently for the relative harmlessness of the treatment.

It must not be inferred from the foregoing statement, however, that insulin shock therapy is harmless when carelessly applied. While in hypoglycemia, the patient is in a potentially precarious condition and must be kept under rigid observation.

We have encountered several complications in applying this treatment, and it will be well to describe them in detail.

1. *Vomiting.*—This complication may be serious if persistent, as it prevents the oral administration of carbohydrates—an indispensable

2. Berze, J.: Die Insulin-Chok-Behandlung der Schizophrenie, Wien. med. Wchnschr. **83**:1365-1369 (Dec. 2) 1933.

3. Küppers, E.: Die Insulinbehandlung der Schizophrenie, Deutsche med. Wchnschr. **63**:377-383 (March 5) 1937.

4. Dussik, K. T., and Sakel, M.: Ergebnisse und Grenzen der Hypoglykämieshockbehandlung der Schizophrenie, Ztschr. f. d. ges. Neurol. u. Psychiat. **155**:351-416, 1936.

5. Müller, M.: Die Insulinschocktherapie der Schizophrenie, Schweiz. med. Wchnschr. **66**:929-935 (Sept. 26) 1936.

necessity, since enough sugar can hardly be given intravenously to cover the usual dose of insulin. We have not often encountered vomiting after nasal feeding but have several times observed patients vomit within two minutes after intravenous termination, before anything had been taken by mouth. These patients responded well to reduction in the insulin dose, to administration of the usual carbohydrates and meal in fractions and to use of a hot water bottle on the abdomen. On one occasion, after a dose of 160 units, a patient vomited repeatedly after termination of shock and finally fell into coma after about four hours. Intravenous injection of dextrose restored him to consciousness immediately, and shortly thereafter he was able to retain food.

2. *After-Shock.*—The patient mentioned in the preceding paragraph, in falling into coma the second time, suffered a serious complication known as after-shock. The secondary period of hypoglycemia results from an intake of carbohydrate inadequate to neutralize the dose of insulin. One must be mindful of such a possibility (though it seldom occurs), as irreversible anatomic changes result from undue prolongation of deep shock. There is an additional hazard in the fact that quiet coma may be mistaken for sleep. When we were studying the therapeutic suitability of protamine zinc insulin we encountered episodes of nocturnal after-shock several times, for this new type of insulin continues to suppress sugar values for thirty-six hours or longer. On one occasion a patient went into convulsions after midnight, but was promptly restored by intravenous administration of dextrose. The liability to after-shock was the chief reason that impelled us to abandon work with the protamine compound and return to the use of regular insulin.

3. *Salivation.*—A moderate degree of salivation is one of the usual phenomena of insulin shock. Occasionally such a copious sialorrhea occurs that the patient threatens to drown himself. Turning the subject on the side or stomach, to allow free drainage, is often enough to combat the condition; however, occasionally shock must be terminated. It is interesting that patients often react as a group from day to day. Thus, on one occasion several patients will salivate copiously, while on another day most of them will have dry mouths. The same is true of extensor spasms. Atmospheric conditions and weather instability may play a more important role in the production of these autonomic phenomena than has heretofore been considered likely. To combat this complication, which so often interferes with the patency of the air passages, we are at present experimenting with use of a nasal catheter in the trachea and with administration of oxygen.

4. *Hunger-Thirst Excitement.*—This is a rare response, which is sometimes encountered early in the treatment, before sensations of

hunger or thirst largely disappear from the hypoglycemic symptomatology. When this complication occurs the patient's wild desire for food so predominates over his other impulses that he may well be described as hunger mad. Sakel said that hunger excitement reacts unfavorably on the patient's psychic pattern and advised immediate termination of shock. We have not encountered serious degrees of this complication, and have had some success in controlling minor manifestations of a similar nature with saccharin diluted to a concentration of 4 grains (0.26 Gm.) to the quart (liter). This solution is about as sweet as the sugar water we employ and may quiet the patient enough for coma to appear.

5. *Tonic Spasms.*—These manifestations have already been described. Typically, tonus of the extensor muscles waxes and wanes. Extension is accompanied by a fast pulse, which slows as the tonus relaxes. We believe that these phenomena depend on cerebral anoxemia. Often they cease and are followed by deep coma; occasionally they become progressively more severe, and then the shock must be terminated.

6. *Sensitivity to Insulin.*—After a patient has been subjected to repeated deep shocks, sensitivity to insulin usually becomes manifest (fig. 2). We believe that the optimum time for a patient to fall into profound coma is from two to three and one-half hours after receiving insulin. When coma appears in less than two hours, particularly when the advent is earlier each day, sensitivity to insulin is present and the dose must be reduced. Failure to heed the warning of early shock may result in such complications as convulsions or extreme difficulty in arousing the patient. The shock dose must often be reduced to one-half or one-fourth its original size during several weeks of treatment, always with resulting deep coma.

7. *Elevation in Temperature.*—The importance of this complication was stressed by Küppers,[3] who expressed the belief that repeated elevation in afternoon temperature is the most sensitive criterion of an overdose. We have followed the usual policy of omitting treatment during any intercurrent infection, even a simple cold in the head.

8. *Difficult Arousal.*—That there is a practical limit of safety to the duration of coma and of hypoglycemia has been shown on a few occasions when we allowed coma to last more than three and one-half hours or hypoglycemia more than seven hours. The patients showed little or no response to intravenous injection of the usual amount of dextrose, and it required several hours to arouse them.

In such an instance the patient was in coma from 8:30 to 12:30 a. m., after a dose of 70 units. The sugar content of the venous blood at this time was 16 mg. per hundred cubic centimeters. Intravenous injection of 12 Gm. of dextrose had practically no visible effect. By 1:45 p. m. the blood sugar had fallen to 14 mg.,

and coma was deeper than at any previous time. The patient eventually responded to more dextrose given by vein, caffeine with sodium benzoate and a tube feeding rich in carbohydrate.

The most effective therapy for difficult arousal appears to be feeding by nasal tube followed by intravenous administration of 1 mg. of epinephrine at the rate of 0.2 mg. in each five minutes (with control of the blood pressure). Patients in this state show little response to intravenous injection of dextrose, even if repeatedly administered.

9. *Convulsions.*—This complication is undoubtedly the "bugbear" of those who use insulin shock therapy. Two types of convulsions may

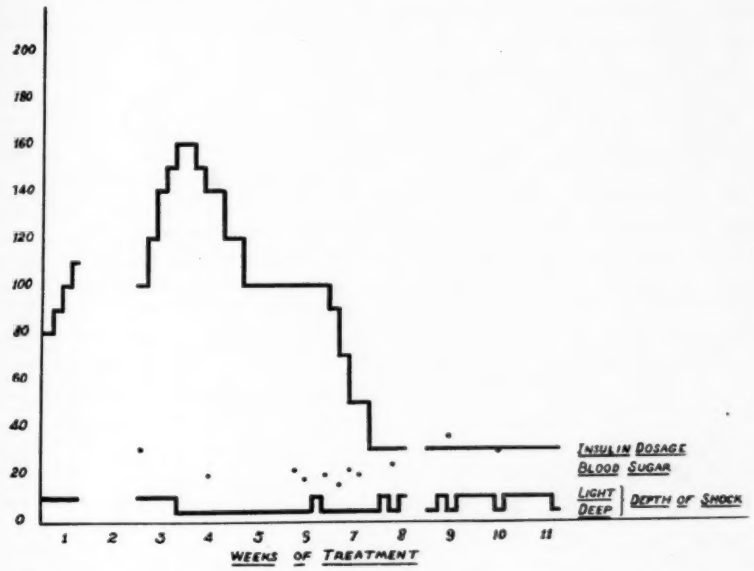


Fig. 2.—Variations in doses of insulin during a typical course of treatment. The dots indicate values for blood sugar at the time of termination of shock (i. e., between 11 a. m. and 12 M.). The doses of insulin are to be read on the left hand column of figures, in units, and the values for blood sugar, on the same column, in milligrams per hundred cubic centimeters.

It is to be noted that 160 units of insulin was required to produce the first deep shock. Sensitivity to insulin then developed quickly, necessitating gradual reduction in the dose to 30 units. With the latter dose the depth of shock was not constant from day to day. The graph also shows that the extent of depression of the blood sugar is largely independent of the size of the dose of insulin.

The patient had been ill for five months when treatment was started. He was discharged in full remission. The gaps in treatment were due to intercurrent illness.

occur—the myoclonic and the epileptiform. There is a regular gradation in severity from single myoclonic twitches to generalized myoclonic seizures, with (usually) little cyanosis. Such episodes, if mild, may be

allowed to continue for some time and may cease spontaneously. Sharply differentiated from these reactions is the true epileptiform fit, which is rare (the incidence in our series being 2.8 per cent of 930 shocks). The seizure begins with a tonic extensor spasm and marked cyanosis and proceeds to a severe clonic phase. Intravenous administration of dextrose is then imperative.

Convulsions appearing in the course of hypoglycemia are not of grave import; they are not necessarily repeated and seldom eventuate in status epilepticus. Nevertheless, certain patients constantly exhibit a low convulsive threshold. An unknown feature of insulin shock therapy is illustrated by the occurrence of convulsions after an adequate intake of carbohydrates—a complication which we are happy to have experienced only twice.

The following history illustrates this difficulty.

CASE 1.—A youth aged 19 had been in a catatonic stupor for a month. We began treatment in December 1936, first with protamine zinc insulin and later with regular insulin. The course was uneventful for three months, deep coma being reached on over 30 occasions. On March 3, 1937, he had a severe convulsion immediately after intravenous termination, but roused promptly. Shock on the next day was uneventful, and the patient ate a large meal after drinking 180 Gm. of sucrose in solution. Three hours thereafter he suddenly had a severe generalized epileptiform convulsion. Six similar fits occurred in the next two hours. Massive doses of sugar administered by vein and nasal tube had no effect, but the convulsions yielded promptly to intramuscular injection of 5 grains (0.325 Gm.) of sodium amytal. There was only one more seizure, but for the next sixteen hours minor episodes involving one limb or the whole body were too numerous to count. The patient remained in a clouded state for a day and then exhibited the first real improvement.

A recent communication by Drabkin and Ravdin (of the University of Pennsylvania)[6] suggested that the degree of hydration has a profound influence on the incidence of convulsions in insulin hypoglycemia. These investigators observed that dehydrated dogs had no rise in cerebrospinal fluid pressure after injection of insulin and that convulsions did not develop. They concluded that the sequence of events leading to convulsions in insulin shock is as follows: (1) severe hypoglycemia; (2) anhydremia; (3) rise in cerebrospinal fluid pressure to a critical level, and (4) convulsions.

THEORY

A theory adequate to explain the success of insulin shock therapy has not yet been advanced and probably will not appear until the pathogenesis of schizophrenia has been elucidated. The neurophysio-

6. Drabkin, D. L., and Ravdin, I. S.: Mechanism of Convulsions in Insulin Hypoglycemia: Interrelationship of Blood Concentration, Cerebrospinal Pressure, and Convulsions, Am. J. Physiol. **118**:174-182 (Jan.) 1937.

logic hypotheses suggested are incapable of proof, and such analytic formulations as those of Glueck [7] are tentative. Certainly, the progressive decerebration which accompanies insulin shock is striking; in some way, repetition of these phenomena of neural disorganization and reorganization gradually blots out the psychopathologic patterns.

RESULTS

Although our experience is not extensive, it has been sufficient to convince us that the claims of European investigators are not unwarranted. In each of the two largest series reported, the number of good remissions secured in cases in which the disease was of less than six months' duration was about 85 per cent.[8]

Our results are as follows:

Patients receiving treatment..... 11
Patients discharged 30

Patients Discharged	Full Remissions	Social Remissions	Improvement	No Improvement
Duration of illness over 2 yrs.....	0	4	2	8
Duration of illness under 1 yr....	8	2	3	3

It may be mentioned that even in cases in which the disease was of long standing and did not improve there were many favorable reactions to individual shocks, but it was impossible to fuse these responses to form a permanently bettered condition.

The histories in the following cases illustrate our grading of recoveries. The first case represents a full, and the second, a social remission.

CASE 2.—Alton E., aged 19, with a moderately tainted inheritance, became ill about September 1936 and was admitted on Oct. 14, 1936, with the history that he had become silent and fearful, thought people were peering in the windows, heard references to himself over the radio and received a message from God through an electric storm. When treatment was started on November 30, he presented a picture typical of hebephrenic pseudostupor, a malignant type of schizophrenia. He was apathetic, slow moving and silent. When left to himself he remained sitting in one place for many hours. He answered questions after much urging only in monosyllables, uttered in an almost inaudible whisper and accompanied by a foolish and inappropriate grin.

Treatment lasted for eight weeks. We used protamine zinc insulin during the first three weeks and then changed to regular insulin, in doses of 50 units daily. This patient, as already mentioned, reacted invariably with mild convulsions if allowed to sink into coma.

Progress was slow but steady. At first, improvement was evident only in the precomatose stage or immediately after termination of shock, at which time the

7. Glueck, B.: Induced Hypoglycemic State in the Treatment of the Psychoses, New York State J. Med. **36**:1473-1484 (Oct. 15) 1936.

8. Dussik and Sakel.[4] Müller.[5]

patient talked normally for a few minutes. Later he began to help around the ward, although he was still almost mute. Still later, he played the guitar or harmonica and sang songs for half an hour or more after termination of the hypoglycemia, only to sink into stupor again. In the last week of therapy improvement became rapid, and it continued to progress after treatment was stopped. On discharge the patient's psychic status showed no detectable abnormality. His emotional reactions were appropriate; he was friendly and grateful to the physicians; his thought content was normal, and he had insight. Most striking was his attitude toward the psychosis; he discussed his hallucinatory experiences and delusions without embarrassment, acknowledged that he had had a mental disease and behaved toward it as one would toward any past physical ailment; that is, he was glad to have recovered, hoped there would be no recurrence and wished to discuss measures to prevent a similar episode. When presented before a staff meeting of the State of Wisconsin General Hospital on March 3, 1937, he gave a clear and full account of his troubles before a large audience, without prompting. In this case one has the impression that the psychosis was actually healed.

CASE 3.—A graduate student of economics at the University of Wisconsin, who had completed all requirements for the degree of doctor of philosophy except the oral examination, had been so plagued by paranoid experiences that he had not been able to do work for the previous eight months. He was continually bothered by anxiety, headaches and various bodily sensations, which he attributed to a poisonous drug which was being administered to him in his bath, in the water of drinking fountains, as a gas at night and in other ways. On admission, he was preoccupied and spent much of his time with his head under the bedclothes. He was not interested in the outside world.

He was treated with protamine zinc insulin only for three and one-half weeks. His usual reaction was limited to hunger and sweating, with moderate shock on only one occasion. Improvement was gradual. The patient became less preoccupied and was interested in outside affairs and in his future; his emotional reactions became more appropriate. On discharge, no abnormal ideas could be elicited by direct questioning and he seemed entirely normal to his friends and associates; we believed, however, that a paranoid substratum was still present, though well concealed. Nevertheless, since Dec. 24, 1936, he has successfully passed his oral examinations, has been awarded his degree and is adjusting well.

CONCLUSIONS

The many details of insulin shock therapy make it an exceedingly complex subject. We dare not be too optimistic until the test of time has been applied to the remissions, but the results in individual cases demonstrate that progress has been made in the therapeusis of schizophrenia.

Dr. Herman H. Shapiro, resident cardiologist at the State of Wisconsin General Hospital, supervised our electrocardiographic investigations.

METRAZOL SHOCK TREATMENT OF THE "FUNCTIONAL" PSYCHOSES

A. A. LOW, M.D.

I. R. SONENTHAL, M.D.

M. F. BLAUROCK, M.D.

MAURICE KAPLAN, M.D.

AND

IRENE SHERMAN, M.D.

WITH THE TECHNICAL ASSISTANCE OF FRANCES C. WHITCOMB, B.S.

CHICAGO

It is said that patients with schizophrenia are not liable to convulsions and that epileptic patients have no tendency to exhibit extreme types of schizophrenic behavior. Glaus [1] in a study of 6,000 patients with schizophrenia at the psychiatric clinic at Zurich, Switzerland, found only 8 who had epilepsy. Steiner and Strauss [2] reported a somewhat higher ratio for the material at the clinic at Heidelberg, Germany. This relative incompatibility of the epileptic and the schizophrenic condition was the starting point for Meduna's [3] endeavor to fight schizophrenic symptoms with production of epileptiform convulsions. Neither Meduna nor the other authors mentioned attempted to correlate the frequency of epilepsy among schizophrenic patients and its incidence in the general population. Grinker [4] placed the frequency of epilepsy "at approximately two per thousand of the population." He continued:

> The army statistics . . . show that in this country at the time of the World War, there were approximately five epileptics in each thousand.

From the Psychiatric Institute (Dr. H. Douglas Singer, Director) of the Research and Educational Hospital, the University of Illinois College of Medicine.

1. Glaus, A.: Ueber Kombinationen von Schizophrenie und Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:450, 1931.

2. Steiner, G., and Strauss, A., in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1932, vol. 9, p. 281.

3. von Meduna, L.: Versuche über die biologische Beeinflussung des Ablaufes der Schizophrenie, Campher-und Cardiazolkrämpfe, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:235, 1935; New Methods of Medical Treatment of Schizophrenia, Arch. Neurol. & Psychiat. **35**:361 (Feb.) 1936.

4. Grinker, R. R.: Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1934, p. 833.

Meduna first used camphor in oil by intramuscular injection but had difficulty in producing paroxysms with the desired promptness and soon replaced it with the more reliable metrazol.

According to von Angyal and Gyarfas,[5] Meduna reported 39 full remissions in 43 patients with schizophrenia of recent onset. Thus, the rate of remission was claimed to reach the almost incredible figure of 90 per cent. Of 67 patients with the chronic form, there were remissions in 22.4 per cent. We have been unable to find these figures in Meduna's papers.

In 1936 von Angyal and Gyarfas [5] published the results of treatment of 45 schizophrenic patients with metrazol. The outcome, as measured by the rate of remission, was by no means as spectacular as that claimed by Meduna. Of 27 patients with the acute or subacute form, with a duration of less than one year, 10 (44.4 per cent) recovered. Of 18 patients with chronic disease, with a duration of more than one year, only 4 (22.2 per cent) recovered.

In view of the recent advent of Meduna's discovery, the literature on metrazol therapy is scant. Finiefs [6] and Gillies [7] discussed the subject in general but did not report their cases. Wahlmann [8] reported 21 cases only. Brousseau's [9] series is the only one, except that of Meduna, to exceed 100 cases. Altogether, we have found in the literature only 286 cases, reported by four observers. It is impossible to draw conclusive inferences from such limited experience as to the scope, promise and limitation of the method. The present report is offered in the hope of clarifying some obscure and disputed points.

MATERIAL AND METHOD

Our series comprises 66 patients whose treatment with metrazol was terminated by the middle of September 1937. Patients with psychoses associated with "organic" disease were excluded. At this institute a system of rotation of treatment is practiced, patients being subjected to one type of treatment after another. On admission, a patient may, for instance, be treated with insulin. If he fails to recover, a shift is made to metrazol. If the second treatment proves unsuccessful, a further shift is made to prolonged narcosis and, if necessary, to fever. To 30 of the 66 patients reported on here metrazol was given first; administration of metrazol to 9 patients was preceded by a course of insulin shocks; to 11, by

5. von Angyal, L., and Gyarfas, K.: Ueber die Kardiazolkrampfbehandlung der Schizophrenie, Arch. f. Psychiat. **106**:1, 1936.

6. Finiefs, L. A.: Induced Epileptiform Attacks as a Treatment of Schizophrenia, Lancet **2**:131 (July 17) 1937.

7. Gillies, H.: Convulsive Therapy in Schizophrenia, Lancet **2**:131 (July 17) 1937.

8. Wahlmann, cited by Brousseau.[9]

9. Brousseau, A.: La therapeutique convulsivante de la schizophrénie, Encéphale **1**:287, 1937.

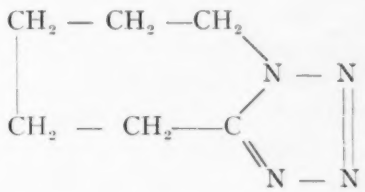
narcosis; to 9, by fever, and to 7, by both fever and narcosis. It is obvious that, because of this rotation, the therapeutic results obtained in our series are not strictly comparable with those reported by other authors.

Dose and Technic of Administration.—Metrazol is administered by the intravenous route in a 10 per cent solution, which is stable and does not require subsequent fresh preparation. We resterilized a sample that had been left unused for eight months and found it effective. As a rule, we give as a first dose 4 cc. of the 10 per cent solution to women and 5 cc. to men, without regard to body weight. According to Meduna, if an injection fails to produce a convulsion, the dose is increased by 1 cc. up to 6 or 7 cc., or higher, at intervals of from two to three days, until a paroxysm results. In the beginning we adopted this procedure and had to wait, in some instances, one or two weeks before we obtained the first seizure. At present we do not hesitate to repeat the injection after about thirty minutes. We did not see ill results from this practice.

It is important to administer the drug with the greatest possible speed, and the use of a 20 gage needle is advisable. Most patients acquire a tolerance, which necessitates a progressive increase in the dose. However, with large doses, the bulk of fluid hampers the rapidity of the injection. We tried to reduce bulk by using a 20 per cent solution, but found that the veins tended to become sclerosed after a few injections.

PHARMACOLOGIC ACTION OF METRAZOL

Hildebrandt,[10] making use of a procedure discovered by Schmidt, produced bicyclic tetrazols from nitrogen-free organic carbon compounds. Several of the tetrazols thus tested proved pharmacologically inert, but pentamethylenetetrazol was found to be a powerful convulsant. The drug had also a marked effect on the respiratory centers. Its peripheral action as cardiac stimulant was assumed by numerous authors, but was disputed by Camp.[11] The proprietary name of pentamethylenetetrazol is cardiazol on the European continent and metrazol in the United States. Its structural formula is:



SEX, AGE AND DURATION OF DISEASE PRIOR TO TREATMENT

Table 1 shows the distribution of the patients with reference to sex, age on admission and duration of the disease prior to admission and prior to treatment. The patients are subdivided into those with

10. Hildebrandt, F.: Pentamethylentetrazol (Cardiazol), Arch. f. exper. Path. u. Pharmakol. **116**:100, 1926.

11. Camp, W. J. R.: The Pharmacology of Cardiazol. J. Pharmacol. & Exper. Therap. **33**:81 (May) 1928.

(1) schizophrenia, (2) other psychoses and (3) affective psychoses and (4) those without psychosis. The term "other psychoses" refers to a miscellaneous group of conditions either unclassified or classified as "psychosis due to metabolic disturbance," "psychosis associated with mental deficiency" and "primary behavior maladjustment." That the distribution on the basis of sex is significantly unequal—21 men and 14 women with schizophrenia and 4 men and 12 women with affective psychoses—is probably due to factors of chance governing the distribution of relatively small numbers. However, the distribution as such reflects the accepted preponderance of males over females in the group of schizophrenic disorders and the reverse in the group of manic-depressive psychoses. The same factor of a small number may explain the numerical discrepancy between the group of 13 women and that of 17 men who finally recovered, although the total numbers were equal.

TABLE 1.—*Distribution According to Sex and Age and Duration of Disease with Reference to Classification and Final Therapeutic Result*

	Number of Patients		Age on Admission, Yr.	Duration of Disease Prior to Admission, Mo.	Duration of Disease Prior to Treatment, Mo.
	Men	Women			
Schizophrenias	21	14	29.9	34.2	38.3
Other nonaffective psychoses	6	6	22.5	20.6	26.1
Affective psychoses	4	12	30.6	16.1	20.1
Patients without psychosis	2	1	34.3	56	62.7
Total number of patients	33	33	28.9	28.3	32.8
Total number of recovered patients	17	13	27.5	15	16.1
Total number of unrecovered patients	16	20	30.2	38.4	43

The average age for the patients who recovered is slightly, but not significantly, lower than that for those who did not recover—27.5 years for the former and 30.2 years for the latter.

There is a marked difference in the duration of disease prior to admission in the various classified groups. The duration for patients "without psychosis" ranges highest, with an average of 56 months, and that for the patients with affective psychoses, lowest, with an average of 16.1 months. For patients who recovered the illness had an average duration of 15 months, and for those who did not recover, 38.4 months. It is difficult to find a valid criterion for the duration of a mental disturbance, since the onset of maladjustment may be insidious and ill defined. At best, the figures represent estimates instead of calculations, and the estimates are tinged largely with the subjective bias of both the informant and the compiler. Though one bears in mind that the figures offered here reflect of necessity a considerable subjective slant, the marked differences between the schizophrenic and the manic-depressive group, on the one hand, and the recovered and the unrecovered

group, on the other, command attention. It is evident that our group of schizophrenic patients, with an estimated average duration of illness of 34.2 months, consisted largely of persons in whom the disease had lasted more than two years prior to admission. Their chances for recovery were obviously poor. That the duration of the disease prior to treatment was generally in excess of the duration prior to admission is explained by the fact that 36 of the 66 patients received the metrazol treatment after previous courses of other forms of treatment.

RATES OF RECOVERY

In table 2 the rates of recovery for the various classified groups are considered in relation to the duration of the disease prior to treatment. The results shown in the table are unmistakable and coincide

TABLE 2.—*Rate of Recovery in Relation to Duration of Disease Prior to Treatment*

Duration of Disease	Schizophrenic Psychoses			Other Nonaffective Psychoses			Affective Psychoses			Patients Without Psychosis			Total		
	Number of Patients	Number of Recoveries	Percentage of Recoveries	Number of Patients	Number of Recoveries	Percentage of Recoveries	Number of Patients	Number of Recoveries	Percentage of Recoveries	Number of Patients	Number of Recoveries	Percentage of Recoveries	Number of Patients	Number of Recoveries	Percentage of Recoveries
1-6 mo.	6	4	66.7	3	3	100	4	4	100	..	..	...	13	11	84.6
6-12 mo.	2	1	50.0	3	1	33.3	4	3	75	..	..	...	9	5	55.6
1-2 yr.	9	1	11.1	3	2	66.7	2	1	50	..	..	...	14	4	28.6
Over 2 yr.	18	2	11.1	3	..	0	6	5	83.3	3	3	100	30	10	33.3
Totals	35	8	22.9	12	6	50	16	13	81.9	3	3	100	66	30	45.5

with what other authors have claimed: The chances of effecting a cure in cases of schizophrenia are best within six months after onset of the disease. The rate of recovery for the contingent of patients with "recent" onset of illness is 66.7 per cent; it falls to 50 per cent when the treatment was begun within twelve months after the breakdown, and to 11.1 per cent when it was begun one or more years after onset of the maladjustment. The results are somewhat better for the group of patients with "other psychoses," but a definite downward trend toward progressively lower rates of recovery is evident. In the group of patients having affective psychoses the tendency is obviously to maintain a relatively high rate of recovery, regardless of the duration of the disease. This is not surprising, since in this group it is not the disease but the present attack that is treated.

Of the group of 16 patients with manic-depressive psychoses, 5 had the manic, 9 the depressed and 2 the involutional type. That 5 of 6 patients whose present attack had lasted more than two years recovered indicates that the rate of recovery for manic-depressive

psychoses does not depend on the duration of the attack. The same holds true for the group of patients without psychosis. Of the 3 patients included in the last group, 1 had an anxiety neurosis. He had spent the greater part of the preceding five years in state hospitals; when out of an institution, he indulged heavily in alcohol in order to escape his fears, as he himself stated. The second patient had lost a fortune in the market crash of 1929 and, since, had suffered from a "shell shock" neurosis. Whether at home or in the street, in company or out of sight of people, the musculature of the face, arms and legs was in continuous motion. The movements of the extremities were choreiform. He was treated with narcosis and with fever, but the choreiform movements and facial grimaces persisted. They were present throughout the day during four months of observation in the ward. After four convulsions induced by administration of metrazol they disappeared. The patient has been entirely free from the movements for six months since leaving the hospital and is now gainfully employed. The third patient was a woman with hypochondriasis of five years' standing. After the fourth metrazol convulsion she ceased making complaints; for the past three months she has resumed care of her family and is free from hypochondriacal complaints and fears.

DIFFICULTY IN DETERMINATION OF RATES OF RECOVERY

Our criteria for pronouncing a patient recovered are threefold: 1. The patient must give evidence that he has given up the complaint which incapacitated him and for which he was committed. 2. He must show good insight. The quality of insight is determined in weekly conferences, which are attended by all patients in the ward who are not bedridden. Patients who have just completed any of the treatments are interviewed by the attending physician and are expected to give a good account of themselves in response to a more or less standardized set of questions. In order to be credited with insight, the patient must state that he knows he has been suffering from a mental disease; he must be able to formulate his previous delusions and to describe the type of devious behavior which he exhibited prior to treatment. In addition, he is required to give evidence that he now realizes that his previous behavior or ideas were "abnormal." One of the questions asked the patient is: "What did you do, say or hear when you came to the hospital that you no longer do, say or hear?" 3. The patient must resume his activity in the community without supervision.

Improvements and "social recoveries" are not considered. Two of our patients treated with insulin are now "socially adjusted" in the community, one for eight months and the other for four months. Both are employed and are adjusting well. However, one still retains the

fears, and the other the suspicions, that led to commitment. These 2 patients are noted in our tabulation as "unrecovered."

We do not pretend that the three criteria are free from possibility of error. They are useful, but by no means infallible. Table 2 shows that, measured by the preceding criteria, 45.5 per cent of the group treated with metrazol recovered (see bottom of vertical "totals" column). Of the 30 patients who recovered, 2 have relapsed thus far, one four months and the other three months after the termination of treatment. On the other hand, 2 patients who at the time of tabulation of the results were considered as not recovered were shortly thereafter discharged as recovered, and are doing well. The ratio of 45.5 per cent is therefore still in force. Of the 30 patients who recovered, 3 have been in the community for six months, 4 for five months, 4 for four months, 6 for three months and the others for more than two or one month. In other words, 17 of 30 recovered patients have maintained unsupervised activity in the community for more than three months to date.

The question arises: Is a recovery rate of 45.5 per cent inferior, equal or superior to the expected rate for spontaneous remissions? Surprising as it may be, this question cannot be answered with any degree of assurance, in the present state of psychiatric knowledge. In the literature we have found reports of four competent follow-up studies on fairly large numbers of patients investigated from four to fifteen years after the first admission to the hospital. Mayer-Gross [12] made a survey of 328 schizophrenic patients who had been admitted to the clinic at Heidelberg in 1912 and 1913. He obtained information on 294 of the patients in 1929, i. e., more than fifteen years after admission. Of the 294 patients, 89 were still in the community "socially adjusted" (*sozial eingepasst*). It is not clear whether the patients had been continuously in the community. The percentage of "good" adjustments here is 30. Fuller,[13] in a study of 242 schizophrenic patients discharged from the New York state hospitals ten years prior to the investigation, found that 29.8 per cent of the men and 41.3 per cent of the women had remained continuously in the community. He did not state whether they were able to perform their activities without supervision. Braatoy,[14] from the clinic at Oslo, Norway, reported on 208 patients with "certain" and 90 with "uncertain" schizophrenia investigated six years after their first admission. His criterion for

12. Mayer-Gross, W., in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1932, vol. 9, p. 534.

13. Fuller, R. G.: What Happens to Mental Patients After Discharge from the Hospital? Psychiatric Quart. **9**:95, 1935.

14. Braatoy, T.: The Prognosis in Schizophrenia, with Some Remarks Regarding Diagnosis and Therapy, Acta psychiat. et neurol. **9**:63, 1936.

recovery was that the patient should be "just as well as before and at full work." The percentage of recovered patients was 20. A recent study of rates of recovery was furnished by Fromenty [15] from the psychopathic department of the general hospital at Tours, France. He did not state the interval between the first admission and the investigation, but from his tables it appears that the patients had left the hospital within a period of from four to fifteen years prior to the study. His percentage of "complete remissions" was 15.

This review of the literature reveals a wide divergence of results and hardly offers a basis of comparison of the present rates for posttherapeutic recovery and the previous rates for spontaneous recovery. If the figures of Mayer-Gross or Fuller are taken as a basis for comparison, the rate for spontaneous recovery is at least 30 per cent after more than ten, or even fifteen, years. It is reasonable to assume that if the percentage of spontaneous recoveries is nearly 30 after ten years or more, the rate must have far exceeded that of 30 per cent one-half year after discharge. Our result of 45.5 per cent for recent posttherapeutic recoveries is, then, at best equal, but probably inferior, to the rate of more than 30 per cent for spontaneous remissions after ten years or more. If our results with the schizophrenic group alone are considered, the rate of 22.9 per cent for posttherapeutic recoveries is clearly eclipsed by the rates for spontaneous remission given by the authors. At present, we can do no more than profess bewilderment, particularly in view of the wide divergence in the respective results of the four investigations cited.

Bewilderment becomes intensified when we consider our own studies on rates of remission. We compared the rates of recovery at this institute for 1937 with those for spontaneous remission for 1935. The policies for admission were deliberately left unchanged during 1937, and we scrupulously avoided favoring any type of selection that was not practiced in 1935. As will be shown in a study shortly to be published on the results of our method of rotation of treatments,[16] the series of patients with "functional" psychoses admitted during 1937 is almost identical with that admitted during 1935 in point of distribution according to age and sex, duration of the disease prior to admission and classification of the patients within the various groups. For these two thoroughly comparable series, the rate of remission for 1935 was 25 per cent, and that for 1937, up to the time of writing, 53.8 per cent.

15. Fromenty, L.: Les rémissions dans la schizophrénie: Statistique sur leur tréquence et leur durée avant l'insulinothérapie, Encéphale **1**:275, 1937.

16. Low, A. A.; Sherman, I. C.; Sonenthal, I. R.; Blaurock, M. F., and Kaplan, M.: Combined (Rotating) Chemotherapy with Insulin, Metrazol, Narcosis and Fever in Functional Psychosis, to be published.

Moreover, the rate of remission for 1935 was not altogether spontaneous, as about half the patients who recovered in that year had been treated with prolonged narcosis.

If a comparison is made of the therapeutic results of metrazol shock and those of sodium amytal narcosis, the superiority of metrazol is clearly demonstrated. During the past five years, nearly 150 patients were treated with prolonged narcosis at the Psychiatric Institute of this hospital. Of these, 44 had manic-depressive psychoses, and 4 were "without psychosis." In other words, 48 of the patients treated with prolonged narcosis belonged to the group of patients who are known to respond favorably to narcosis therapy. Of the 48 patients, 21 were considered to be cured immediately after termination of the treatment. The rate of recovery was 43.8 per cent. In our present group treated with metrazol, the patients with manic-depressive psychoses numbered 16, and those without psychosis, 3. Of these 19 patients 16 recovered. The rate of recovery was 84.2 per cent. When it is added that the narcosis treatment has a relatively high mortality rate while with the metrazol method 1 fatality only has been reported to date (von Angyal and Gyarfas), the superiority of metrazol to narcosis therapy seems established.

CONVULSIVE THRESHOLD

Table 3 records the convulsive threshold for the patients as measured by a variety of reactions to the injection of metrazol. Von Angyal and Gyarfas [5] and Brousseau [9] maintained that patients with a lowered threshold (*aptitude convulsivante; bessere Krampfbereitschaft*) have a better rate of recovery. Table 3 offers three measures for the convulsive threshold: (1) the number of convulsions per ten injections, (2) the size of the first convulsive dose and (3) the interval between the first injection and the first convulsion. The data demonstrate that the number of convulsions per ten injections is practically the same for all groups of classification and that it differs little for the recovered and for the unrecovered patients. In all these groups the ratio is consistently about seven convulsions per ten injections. This result is in marked contrast with the statement of von Angyal and Gyarfas [5] that "in patients who obtained full remissions convulsions were released by 60 per cent of all injections, in those who obtained social remissions by 49 per cent and in those who did not recover by 45 per cent." The table shows further that no significant difference exists in the average first convulsive doses for the three main groups of the classification. Whether the difference between the first convulsive dose for the recovered patients (4.1 cc.) and that for the unrecovered patients (5 cc.) is significant is difficult to state. The only undoubted point of differentiation which the table offers is with regard to the

interval between the first injection and the first convulsion. In the schizophrenic group, 77.1 per cent of the patients reacted with a convulsion immediately after the first injection. For the patients with "other psychoses" the percentage is 41.7; for the patients with manic-depressive psychoses and those without psychosis the combined percentage is 52.6. In other words, the schizophrenic patients, with the lowest rate of recovery, scored lowest for the convulsive threshold, which suggests that the readiness with which a convulsion is released in response to the injection is in inverse ratio to the probability of recovery. In confirmation of this, the table shows further that of the 30 patients who recovered only 50 per cent had a convulsion after the first injection, while the corresponding percentage for the unrecovered

TABLE 3.—*Reaction to Metrazol (Convulsive Threshold) with Reference to Classification and Final Therapeutic Results*

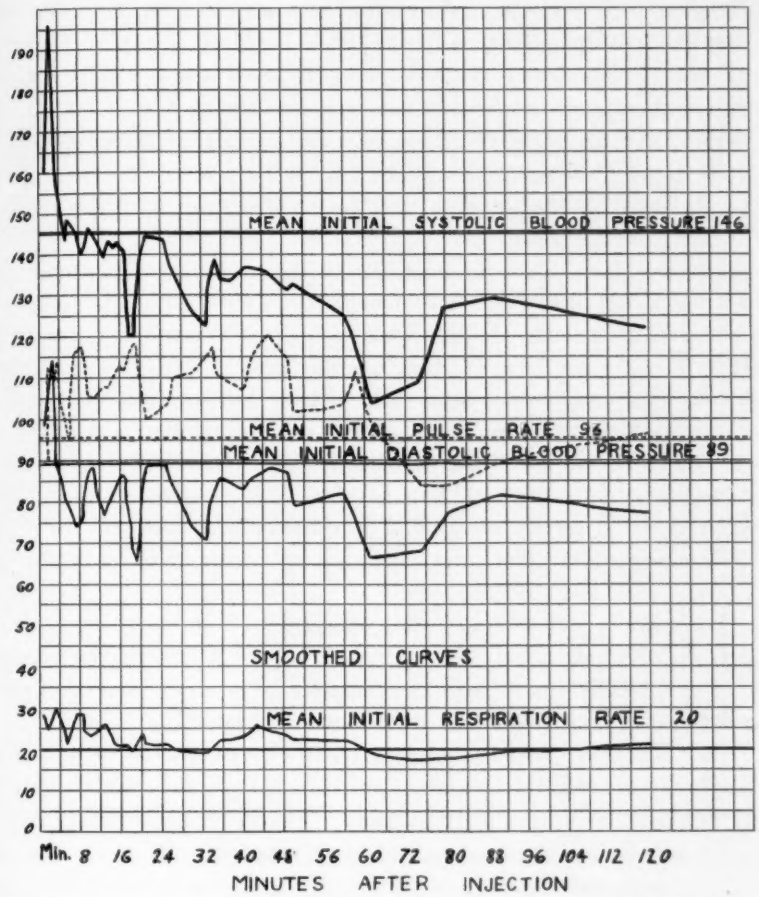
	Number of Patients	Number of Injections per Patient	Number of Convulsions per Patient	Number of Convulsions per 10 Injections	First Convulsive Dose, Cc.	First Convulsion After First Injection		First Convulsion After Second Injection		First Convulsion After Three or More Injections	
						Number of Patients	Percentage of Patients	Number of Patients	Percentage of Patients	Number of Patients	Percentage of Patients
Schizophrenia	35	18.2	12.5	6.9	4.9	27	77.1	5	14.3	3	8.6
Other nonaffective psychoses	12	15.4	11.3	7.4	4.4	5	41.7	5	41.7	2	16.7
Affective psychoses and patients without psychosis	19	12.8	9.0	7.0	5.2	10	52.6	4	21.1	5	26.3
Total number of patients	66	16.4	11.5	7.0	5.0	42	63.6	14	21.2	10	15.2
Total number of recovered patients	30	12.6	8.1	6.8	4.1	15	50.0	10	33.3	5	16.7
Total number of unrecovered patients	36	19.1	13.5	7.1	5.0	27	75.0	4	11.1	5	13.9

patients was 75. Our experience, then, is the reverse of the claims made by the aforementioned authors.

PHYSIOLOGIC OBSERVATIONS

1. *Vital Signs.*—The accompanying chart plots the smoothed curves for pulse rate, respiratory rate and blood pressure for 10 patients immediately before and for about two hours after a paroxysm. Recording is impossible, of course, during the paroxysm, with ordinary clinical means of observation. During the first ten minutes after termination of the paroxysm the observations were made at the rate of about one per minute. During the second ten minute period they were carried out at intervals of about two minutes. Thereafter, they were recorded every five minutes, up to one hour after the paroxysm. During the second hour five observations were made, and a few scattered recordings were added during the third hour.

Except in the case of respiration, the mean initial rate is conspicuously high. For the systolic blood pressure it is 146 mm. of mercury; for the diastolic pressure, 89 mm.; for the pulse, 96, and for respiration, 19.5. Shortly after termination of the spasm, the mean systolic blood pressure is recorded at 160 mm.; it then rises quickly to 197



Mean values for systolic and diastolic blood pressures and pulse and respiratory rates for 10 patients during and after paroxysms induced by metrazol. The figures along the abscissa represent the number of minutes after the injection.

mm. During the following ten minutes it fluctuates between 170 and 142 mm.; but values above 150 mm. predominate. Fairly wide fluctuations are still in evidence up to one hour after the paroxysm, but the general level keeps within the range of from 130 to 140 mm. A gradual and constant decline sets in about eighty minutes after the

paroxysm and reaches average values at the end of the second hour. The pulse, respiration and diastolic blood pressure show analogous behavior.

It seems legitimate to conjecture that the marked elevation of the mean initial rates reflects an attitude of fear or anxious expectation in the patient and that the failure of the pulse rate and blood pressure to return to their average levels, even after more than one hour, connotes an intense disturbance that is by no means fleeting.

2. *Blood Chemistry.*—Table 4 gives the means and standard deviations for the p_H, the carbon dioxide content, the dextrose and calcium levels and the leukocyte counts before and after the paroxysm for 10 patients treated with metrazol. The correlative values used as controls were obtained for the same patients on a subsequent or preceding day without a convulsion.

The blood was drawn under oil from the cubital vein without stasis and transferred under oil into constricted tubes which contained 3 drops of a 20 per cent solution of potassium oxalate. These tubes were kept on ice until the examination was made. The blood for determination of calcium was placed in a separate tube and allowed to clot.

The p_H was determined according to the method described by Myers and Muntwyler;[17] the carbon dioxide content was estimated by the method of Stadie and Van Slyke.[18] The method employed for determination of dextrose was that of Shaffer and Hartman, as modified by Somogyi.[19] The total calcium levels were determined by the Kramer-Tisdall method.[20]

Slides for a differential count were made from the blood drawn under oil. The oil caused the nuclear chromatin to become so pyknotic that the Schilling index was not reliable. The cells were therefore merely divided into granulocytes and mononuclears.

Table 4 shows that the samples obtained as controls from the 10 patients maintained fairly stable values both for the blood chemical determinations and for the cell counts. The fasting values just prior to injection of metrazol also fall approximately within the normal range of the samples used as controls. Ten minutes after a paroxysm

17. Myers, V. C., and Muntwyler, E.: The Colorimetric Estimation of the Hydrogen Ion Concentration of Blood, J. Biol. Chem. **78**:243, 1928.

18. Stadie, W. C., and Van Slyke, D. D.: Carbon Dioxide Content and Capacity in Arterial and Venous Blood Plasma, J. Biol. Chem. **41**:191, 1920.

19. Somogyi, M.: A Reagent for the Copper-Iodometric Determination of Very Small Amounts of Sugar, J. Biol. Chem. **117**:771, 1937.

20. Tisdall, F. F.: A Note on the Kramer-Tisdall Method for the Determination of Calcium in Small Amounts of Serum, J. Biol. Chem. **56**:439, 1923.

the mean value for the p_H falls to 7.17, that for the carbon dioxide content to 34.1 volumes per cent and that for the calcium to 8.78 mg. per hundred cubic centimeters. These values express clearly a sudden change to acidotic levels and a disturbance in mineral metabolism. After one hour an ascent toward the previous normal levels is noticeable, and after another hour the ascent is completed. The increase in the dextrose level ten minutes after a convulsion and the coincident changes in the leukocyte count are hardly significant, although the increase in mononuclears may be of importance.

TABLE 4.—*Means and Standard Deviations for the p_H and Carbon Dioxide, Dextrose, Calcium and Leukocyte Values of the Blood Before and After Paroxysms*

		Means and Standard Deviations for	
		Ten Patients Treated with Metrazol	Ten Control Patients
p_H	Fasting	7.34 ± 0.023	7.35 ± 0.035
	After 10 min.	7.17 ± 0.048	7.34 ± 0.031
	After 1 hr.	7.29 ± 0.028	7.33 ± 0.044
	After 2 hr.	7.32 ± 0.036	7.34 ± 0.043
Carbon dioxide, vol. %	Fasting	57.5 ± 6.70	56.6 ± 3.80
	After 10 min.	34.1 ± 6.42	59.7 ± 5.97
	After 1 hr.	47.1 ± 5.70	59.3 ± 4.04
	After 2 hr.	56.4 ± 4.52	57.4 ± 5.82
Dextrose, mg. per 100 cc.	Fasting	73.4 ± 5.76	73.8 ± 5.26
	After 10 min.	90.9 ± 12.55	74.2 ± 6.44
	After 1 hr.	81.1 ± 6.20	73.1 ± 4.92
	After 2 hr.	72.7 ± 8.15	74.4 ± 6.82
Calcium, mg. per 100 cc.	Fasting	10.63 ± 1.080	9.76 ± 0.634
	After 10 min.	8.78 ± 1.373	9.79 ± 0.418
	After 1 hr.	9.21 ± 0.670	9.88 ± 0.584
	After 2 hr.	9.44 ± 0.373	9.94 ± 0.441
White blood corpuscles per cu. mm.	Fasting	7,145 ± 864	7,510 ± 790
	After 10 min.	11,767 ± 3,267	7,400 ± 822
	After 1 hr.	8,533 ± 1,963	7,690 ± 834
	After 2 hr.	8,170 ± 1,056	7,600 ± 1,061
Granulocytes, percentage	Fasting	69.7 ± 7.16	63.2 ± 8.56
	After 10 min.	56.1 ± 15.90	63.8 ± 5.84
	After 1 hr.	65.3 ± 12.30	63.6 ± 5.08
	After 2 hr.	74.0 ± 7.00	60.9 ± 9.25
Mononuclears, percentage	Fasting	29.5 ± 6.90	35.4 ± 8.68
	After 10 min.	42.9 ± 15.50	34.9 ± 5.65
	After 1 hr.	33.9 ± 12.10	35.6 ± 5.52
	After 2 hr.	25.3 ± 6.42	31.8 ± 7.71

Comment: We shall avoid inferences with regard to the possible meaning of the laboratory finding, because the observations are too few for valid conclusions. Premature speculations, however, have already crept into the literature. Steinfeld and Gerber [21] found a marked reduction in the oxygen content of the blood immediately after a metrazol paroxysm and, if we correctly understand the authors' none too clear presentation, a rise during insulin coma. From these observations the investigators drew far-reaching conclusions as to the etiologic

21. Steinfeld, J., and Gerber, L.: Oxygen Content of the Blood During the New Treatments for Schizophrenia, Illinois M. J. **72**:351, 1937.

factors and prognostic possibilities. Obviously, the only conclusion that is permissible from studies of this kind is that metabolism is more or less violently disturbed both by metrazol convulsions and by insulin coma. The disturbance affects many phases of metabolism: the acid-base equilibrium, the oxygen and carbon dioxide contents, the metabolism of minerals and, presumably, the protein elements and the water balance. Disturbance of the acid-base equilibrium was the main alteration we detected. Any etiologic or prognostic claim based on such isolated investigations on metabolic part situations is valueless, and even misleading.

3. *Basal Metabolic Rates.*—Determinations were made for 5 patients, immediately prior to a paroxysm and one-half, one, two and three hours after termination of the convulsion. The results are shown in table 5. There is a marked rise after half an hour, ranging from

TABLE 5.—*Basal Metabolic Rates for 5 Patients Before and After the Paroxysm, Expressed in Percentages*

	W. B.	L. B.	A. G.	F. S.	C. B.
Before paroxysm	+19	— 5	— 6	—19	— 1
After paroxysm					
30 minutes	+60	+23	+25	+27	+59
1 hour	+ 2	+13	+ 3	+16	+31
2 hours	+24	+ 2	— 5	— 0	+26
3 hours*	+24	+19	+ 4	+24	+15

* The three hour readings may be assumed to be unreliable, as the patients all tended to become restless as the hours advanced.

about 30 to 60 per cent. In subsequent readings the metabolic rate decreases, but maintains a fairly high level, which in 3 of the 5 patients is considerably in excess of the preparoxysmal level.

COMPARISON OF METRAZOL PAROXYSM AND GRAND MAL ATTACK IN CRYPTOGENIC EPILEPSY

Although in our experience the metrazol paroxysm differs in various essentials from a grand mal attack, we were surprised to find in the literature a striking unanimity of assertion that the metrazol spasm is identical in course and symptomatology with the grand mal seizure. Hager,[22] in a preliminary report, termed the metrazol convulsion a "classic epileptic attack." Wichmann [23] stated that the metrazol paroxysm produced in patients with idiopathic epilepsy "is equal throughout to

22. Hager, F.: Ueber medikamentöse Behandlung der Schizophrenie, Deutsche med. Wchnschr. **63**:1438 (Sept. 17) 1937.

23. Wichmann, B.: Ergebnisse und Bemerkungen zur Frage des durch Cardiazol künstlich hervorgerufenen epileptiformen Anfalles, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:582, 1937.

the spontaneous seizure." Langelüddeke [24] voiced the same opinion. Finiefs [6] expressly stated that the fit "has all the dramatic appearance of a grand mal attack." Gillies [7] said: "Usually the convulsion is a typical major epileptic fit." Janz [25] stated: "The attack offers the classic symptoms of the major epileptic fit." None of these authors attempted to substantiate his assertions by means of detailed description. That there are differences between the attack induced by metrazol and that spontaneously released during a major epileptic fit is demonstrated by the following description.

1. *Aura.*—Generally speaking, what may be considered as aura varies from one patient to another. It is our impression that the sensation is relatively constant in successive convulsions of the same patient. A few descriptions given by patients are cited.

M. B., with an involutional depression, who recovered, made identically the same statement after two of three convulsions. "I saw fire; red fire." A. H., also with an involutional psychosis and good recovery, described her sensation as "Something like a motor in my head." J. D., a catatonic patient who recovered, volunteered the information: "It's like electricity in my head and chest, and I could smell the medicine for a long time." Some patients claimed that the "head gets dizzy." Others experienced an "electric shock." One patient recalled a "pumping feeling in the brain." Another said: "I felt like I had licorice in my mouth." A highly articulate manic patient said: "I get a feeling of being charged with electricity, and I feel very light. Then, all of a sudden, bright lights appear before my eyes; they range in diameter from ½ to 1½ inch, and they seem to get farther away until I am gone." A patient said: "The first thing that treatment does is to make me want to pray. I can feel that stuff going up my arm, and when it hits my heart I feel like I am dying. Light flashes before my eyes; I bat my eyes real fast, and then I pass out." Some patients, when questioned about their recollection, merely stated that what they experienced is indescribable, or that they "just fainted and passed out." It is our impression that auras involving vestibular function (dizziness, fainting and "spinning around") are most frequent; that auras pertaining to visual function (light, flashes, blurring) are next, and that auras with auditory, olfactory and gustatory components (noise, explosion; "smoky feeling," "funny" smell; licorice, minty taste) are less frequent, but common. The sensation of an electric current was frequently mentioned.

2. *Initial Cry and Cough.*—Some patients utter a cry immediately preceding the convulsion; others produce a cough, and still others, something like a gurgling sound. The cough is the most common. If a cry ushers in the first convulsion it is almost certain to initiate all subsequent convulsions. The same is true of the cough. However, in

24. Langelüddeke, A.: Ueber die differentialdiagnostische Bedeutung der Cardiazolkrämpfe, Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:203, 1936.

25. Janz, H. W.: Die diagnostische Verwertbarkeit einiger Methoden zur Provokation epileptischer Anfälle, Arch. f. Psychiat. **106**:267, 1937.

some patients the pattern changes or alternates in succeeding spasms; the patient who today emits a cry may on another day produce a cough, and vice versa.

3. *Convulsive Stage.*—We attempted to record the sequence of convulsive manifestations as accurately as possible by parceling out discrete phases of the paroxysm to separate observers. One limited himself to observing the head and face; one, the upper extremities, and one, the lower extremities. Each observation was timed with a stop watch. Even so, the material collected is insufficiently accurate, though it accords with appearances shown in moving picture films. A final verdict must be left to slow motion kinematographic studies, which are now in progress. Our present observations indicate that the pattern of the paroxysm is not uniform for all patients; however, some recurring sequences are discernible.

The following is the most common sequence observed: After the initial cry or cough the patient usually raises the head; there is a flutter of the eyelids, and the features reflect an expression of bewilderment or consternation. Suddenly the arms are thrust forward and thrown about in a few wild movements. The trunk and legs may be raised, and the entire body may be in motion, the gluteal region being used as a fulcrum. After two or three sequences of such violent jactitations, the trunk and legs fall back, and the first phase of the paroxysm is over. This sequence of movements is the type most frequently seen in the first phase. The movements give an impression of the trunk and extremities merely being thrown about, without any well defined pattern or rhythm. Sometimes, the motor sequence described is replaced by a few rhythmic clonic jerks, especially of the arms.

The second phase, as a rule, is ushered in by spasmodic opening of the mouth, which, persisting for a number of seconds, leaves ample time for insertion of a tongue protector. Suddenly, the trunk and extremities pass into tonic contraction. The rigidly extended arms are held in front of the body; the legs are raised, and the hands and feet pass into carpopedal spasm. Frequently, one arm is held in rigid flexion, and the other, in equally rigid extension. This tonic phase lasts about ten or fifteen seconds and then passes into the clonic stage.

The clonic oscillations may begin in one joint and spread until all other joints become involved, or all joints of both extremities may begin the convulsive movements simultaneously. However, more often the spasm begins with slight tremors in the fingers and toes, which are quickly followed by spasmodic movements of the wrists and ankles. After a second or two the convulsion reaches the elbows and knees and, finally, the hips and shoulders. Now the entire body shakes, with quick flexion-extension sequences playing over all joints. In the upper extremities adduction and abduction sequences are sometimes seen.

Occasionally, one side of the body is seized with convulsions, and then the other, after a brief interval.

As the tonic phase develops, the mouth as a rule is closed. In some patients, however, closing the mouth falls within the period of clonic convulsions. If the mouth is kept open well into the clonic phase, it is almost invariably due to dislocation of the jaw. The tongue is seldom protruded, and biting the tongue is comparatively infrequent, even when protection is insufficient.

Conjugate deviation of the eyes is an almost constant observation. It is usually seen in the beginning of the tonic interval and continues to the end of the paroxysm. On 47 occasions it was noted that the eyes turned seven times to the right, nine times to the left, thirteen times to the right and upward and fourteen times to the left and upward. On four occasions the deviation was straight upward without a noticeable right or left component. It is interesting to note that in this unselected group of observations, there was no preference for either the left or the right side. Moreover, it happens at times that the deviation is to the left at the beginning of the spasm and subsequently swings to the right, and vice versa. Conjugate deviation of the head is observed at times. Sometimes we saw internal strabismus of one eye, usually the right. The pupils as a rule are maximally dilated and unresponsive to light at the beginning of the tonic phase. They remain so to the end of the paroxysm. Soon after the paroxysm is over, reaction to light is restored and the dilatation is reduced.

At the end of the clonic phase, but more frequently, it seems to us, during the post paroxysmal stage, a viscid mucoid discharge is seen at the orifice of the penis. Microscopic examination of several samples revealed living spermatozoa. Involuntary urination is more apt to occur in the clonic than in the postparoxysmal phase. Involuntary defecation was not noted in any instance.

Salivation is almost uniformly present, but hardly ever reaches the proportions of "foaming at the mouth." In all instances which we observed salivation began at the end of the paroxysm. The process is one of forceful projection of saliva, coincident with the spasmodic respiratory movements. Usually, the saliva is rhythmically blown out and drawn in in the form of bubbles.

During the tonic phase the face is flushed; the flush may extend to the abdomen. As the clonic phase sets in, cyanosis develops and continues throughout the clonic spasm, and sometimes beyond it. Coincident with the cyanosis, the flush turns to pallor. Usually, the pallor is followed by a period of apnea, which lasts a few seconds.

A marked pilomotor reaction, covering the extremities, abdomen and chest, is frequent. Sweating, if present, is seldom profuse.

The first "throwing-about movements" usually appear about ten or fifteen seconds after the injection. The intermediate tonic phase lasts also about ten or fifteen seconds, and the clonic convulsions, about thirty or forty-five seconds. As a rule, the entire spasm is over within about sixty or seventy seconds.

Brief after-twitches occur frequently within ten or twenty seconds, sometimes within a minute or two after cessation of the paroxysm.

POSTPAROXYSMAL BEHAVIOR

After the paroxysm some patients lie flat on the back, practically motionless, with the eyes closed. A forceful respiratory movement of the chest, with attendant salivation, is almost the only visible phenomenon. Other patients throw themselves about, thrust out the legs and arms, raise the trunk, let it fall, raise it again, etc. The impression is one of intense motor restlessness without any well defined pattern. A sizeable number of patients, however, present a striking motor pattern in the leg movements. In these instances the legs are alternately moved about or held quietly in a manner that recalls the "frog leg position." The thighs are abducted and the legs adducted, so that the knees jut out from both sides of the body. The lower extremities then form a rhombus, and the designation "frog leg position" may be the proper term for the phenomenon.

An observation we made in a number of patients is worth recording. Soon after termination of the paroxysm, during the period of motor restlessness, the hands pass to the pubic region and rub or pat the scrotum. Sometimes the adductor muscles of the legs are patted. One patient refused to undress completely prior to an injection, giving as a reason the presence of nurses. He was allowed to keep "shorts" on. It was then observed that during the period of motor restlessness he passed the hand underneath the "shorts," down to the scrotal region, and performed the patting movement. Patting of the pubic region or of the adductor muscles was observed in 21 men and in only 9 women.

In the postparoxysmal stage the tonus of the lower extremities remains increased for a few minutes, but there is practically never spasticity of the upper extremities. A positive Babinski reflex is sometimes elicited, unilaterally or bilaterally, but its occurrence is sporadic and fleeting.

The majority of patients are stuporous after the paroxysm. The stupor soon gives way to a mild daze, which may continue for hours. Some patients pass into a state of confusion in which they are disoriented and incoherent. One patient with an involutional psychosis remained in a markedly confused state for several days in succession and made a complete recovery on emerging from the confusion.

PSYCHOLOGIC OBSERVATIONS

The frequent dazed condition and the occasional confusion following a paroxysm have been mentioned. Prior to the paroxysm most patients evince fear. The fear assumes occasionally the proportions of an obsession, or even of panic. Patients beg not to be treated. They implore physicians and nurses to save their lives. Sometimes they resort to ruses and tricks, ask to be permitted to go home for a week-end and, if given permission, refuse to return. One patient innocently asked: "Do you think if I offer to wash Dr. B's car I will not have to take the treatment?" This fear of the treatment has also been noted in patients treated with insulin and has attracted the attention of investigators. The theory has been advanced that it is perhaps the fear, not the treatment, that produces the recovery. In view of this theorizing, it seemed desirable to make a count of the fear reactions of the patients in our series. If the theory of the curative action of fear is correct, it is to be expected that the most pronounced and most frequent fear reactions will be found in patients who recover. Mindful of the fact that we were likely to inject our personal views into the issue, we instructed the nurses to make note of fear reactions under the headings "always fearful of treatment," "usually fearful," "indifferent" and "spontaneously asking for treatment." Of 66 patients treated with metrazol, 30 were labeled as "always fearful;" of these, 10 recovered and 20 failed to recover. Of 26 patients who were "usually fearful," 11 recovered. Of 10 patients who either were "indifferent" or "spontaneously asked for treatment," 9 recovered. If any conclusion is to be drawn from this tabulation it is obviously the reverse of the aforementioned theory; patients who subsequently recovered exhibited less fear of the treatment than those who did not recover.

COMPLICATIONS

Dislocation of the jaw during a convulsion is common. In some patients the dislocation occurs in practically every paroxysm. As already mentioned, if a patient's mouth remains open during the greater part of the paroxysm mandibular luxation should be thought of. Reposition is effected with ease by the ordinary maneuver of pushing the jaw down and toward the occiput. It is advisable to have a thumb guard ready for this purpose, which preferably should be of leather. Three patients suffered dislocation of a shoulder. This complication is of importance in that it renders further treatment difficult or impossible. In 1 patient avulsion of the greater tuberosity of the left humerus was observed immediately after a convulsion.

Nausea and vomiting were not uncommon after the first convulsion. As a rule, succeding paroxysms brought disappearance, first, of the vomiting, and then, of the nausea.

Elevation of the rectal temperature to 101.2 F. and of the pulse rate to 120 were observed in 1 patient. The condition lasted for a few hours after the convulsion and then disappeared.

CONTRAINDICATIONS

We have had no serious mishap of any kind. The precautions taken are based on general considerations and not on knowledge of possible dangers inherent in the treatment. Prior to treatment, patients are given a routine examination, including basal metabolic readings and studies of the blood chemistry; in addition, an electrocardiogram and a roentgenogram of the chest are made. We have withheld treatment from several patients because of electrocardiographic evidence of myocardial damage. However, 1 patient had slurring of the QRS complex and a diphasic T wave in leads I, II, and III; she was, nevertheless, placed under treatment, in response to her urgent pleadings and those of her husband. She was given first a dose of 4 cc. of a 10 per cent solution; convulsion was not produced until a dose of 5 cc. was reached. She reacted with severe vomiting and nausea to the first convulsion, and treatment was interrupted for a short time. When it was resumed there was no complication, and a course of eighteen injections with fifteen convulsions, was completed, with good therapeutic results and no complication.

CONCLUSIONS

1. Metrazol shock treatment in this series of patients with "functional" psychoses gave a relatively high rate of recovery for persons with manic-depressive conditions and those "without psychosis." For the schizophrenic group, treatment yielded a relatively high rate of recovery only if given within six months after onset of the disease. However, in the absence of knowledge concerning rates for spontaneous remission it is at present impossible to gage accurately the therapeutic value of the convulsive treatment.

2. For manic-depressive conditions the superiority of the metrazol treatment to that with prolonged narcosis appears evident; it has increased the rate of remission and reduced the incidence of dangers and complications.

3. The claim advanced by some authors that the outlook for recovery is proportional to the "convulsive threshold" of the patient is not substantiated by the present investigation.

4. Contrary to the assertion of some investigators, the metrazol paroxysm differs in several respects from the "grand mal" attack of cryptogenic epilepsy.

MECHANISM OF MIGRAINE HEADACHE AND ACTION OF ERGOTAMINE TARTRATE

J. R. GRAHAM, M.D.
AND
H. G. WOLFF, M.D.
NEW YORK

The observation that administration of ergotamine tartrate regularly and promptly ends the migraine headache introduced a new approach to the experimental study of this syndrome (Tzanck,[1] Lennox and von Storch,[2] O'Sullivan [3]). With this effective tool the attack can be sufficiently shortened to permit convenient analysis of certain changes that take place in the transition from the peak to the termination of the headache. Because ergotamine tartrate predominantly affects smooth muscle, inquiry concerning its action during migraine headache was centered on the cranial blood vessels. The experiments described here were performed when the phenomena which characterize the onset of an attack, namely, scotomas, blurring of vision, paresthesias and aphasia, had already passed and had been supplanted by headache. Hence these results have no bearing on preheadache phenomena. They concern only the origin of migraine pain.

MATERIAL

Experimental analyses were made during thirty-two attacks of migraine occurring in sixteen subjects. Additional, less complete, observations were made during twenty attacks in six other subjects. The diagnosis of migraine was based on a history of periodic headache, unilateral in onset, often preceded by visual phenomena and accompanied by nausea and sometimes by vomiting. Such periodic headache often occurred in other members of the family. Fifty series of observations and records were made on forty-six subjects used as controls who were either healthy laboratory workers or patients in the general medical wards of the New York Hospital and who, after having been told the nature of the procedure, volunteered their cooperation.

From the New York Hospital, Department of Medicine, and Cornell University Medical College.

1. Tzanck, A.: Le traitement des migraines par le tartrate d'ergotamine, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1057, 1928.

2. Lennox, W. G., and von Storch, T. J. C.: Experience with Ergotamine Tartrate in One Hundred and Twenty Patients with Migraine, J. A. M. A. **105**: 169 (July 20) 1935.

3. O'Sullivan, M. E.: Termination of One Thousand Attacks of Migraine with Ergotamine Tartrate, J. A. M. A. **107**:1208 (Oct. 10) 1936.

METHOD

Pulsations of the temporal and occipital branches of the external carotid artery were recorded by means of tambours placed on these arteries where they could be palpated under the skin (Clark, Hough and Wolff [4]). The tambour was connected to a Frank capsule by means of a thick rubber tube. A beam of light from a slit lamp was thrown on a mirror on the thin rubber diaphragm of the capsule in such a way that it was reflected into the slit of a camera, to be recorded on moving bromide paper. Any pulsation transmitted to this air system by the artery caused the mirror to deflect the beam of light through an arc, the length of which was proportional to the force of the impulse.

In the same way, pulsations of the intracranial and intravertebral arteries, as reflected in the spinal fluid, were recorded by means of a Frank capsule connected directly with a needle in the lumbar subarachnoid space. A timer was so arranged that it recorded intervals of seconds on the bromide paper, thus permitting determinations of pulse rate. Blood pressure readings were made at frequent intervals, and in ten experiments the skin temperatures of the ear, cheek, temple and hand were measured by a Hardy radiometer (Hardy [5]).

Changes in the intensity of the headache were estimated by the patient and recorded in terms of "plusses," with the understanding that 10 + represented the "most severe" headache. The patient allotted a suitable number of "plusses" to the intensity of his pain at the beginning of the period of observation and subsequently reported in terms of "plusses" such changes in intensity as took place. The subject rested comfortably on a couch, and at least three records of the amplitude of pulsations of the arteries were made at intervals of several minutes, to obtain suitable measurements as controls. With each control measurement the subject was asked to estimate the intensity of his headache in terms of "plusses," and simultaneously blood pressure readings were taken.

EXPERIMENTAL RESULTS

A. *Relation of Headache to the Effect of Ergotamine Tartrate on Certain Branches of the External Carotid Artery.*—After the observations made as controls, ergotamine tartrate [6] (from 0.37 to 0.5 mg.) was injected intravenously and, as already described, records of the pulsations of the temporal or the occipital artery on the affected side were made at frequent intervals until the headache was abolished. In twenty such experiments the injection of ergotamine was followed by decrease in amplitude of the pulsations. The maximal reduction was

4. Clark, D.; Hough, H., and Wolff, H. G.: Experimental Studies on Headache: Observations on Headache Produced by Histamine, Arch. Neurol. & Psychiat. **35**:1054 (May) 1936; A. Research Nerv. & Ment. Dis., Proc. **15**: 417, 1934.

5. Hardy, J. D.: The Radiation of Heat from the Human Body: I. An Instrument for Measuring the Radiation and Surface Temperature of the Skin, J. Clin. Investigation **13**:593, 1934.

6. Sandoz Chemical Works, Inc., of New York, furnished us with gynergen for these experimental studies.

84 per cent of the original amplitude, the minimal 18 per cent and the average approximately 50 per cent. This drop usually began immediately, but in some instances its onset was delayed for from ten to fifteen minutes. The maximum drop was obtained in from about thirty to forty minutes in most instances.

This marked decrease in the amplitude of the temporal or occipital pulsations bore a close relation to the decline in the intensity of the headache. In sixteen of the twenty experiments the amplitude of pulsations declined with the diminishing intensity of the headache. If the amplitude of pulsations decreased slowly, headache likewise diminished slowly. If the amplitude dropped precipitously, the headache was ended promptly. Two representative examples are shown graphically in figures 1 and 2. In figure 1 is the record of a headache which was terminated in ten minutes, and in figure 2, that of a headache which diminished gradually during the course of an hour. It will be noticed that the decrease in amplitude of the pulsations paralleled the decline in intensity of the headache, both in time and in degree.

In four subjects this relationship was doubtful or was not apparent in the first observations, although such a correlation between intensity of headache and amplitude of pulsations was evident during subsequent observations in these and all other subjects used in this study.

Similar observations made on a group of thirty-four subjects used as controls showed an almost identical reaction of the arteries to ergotamine tartrate. The average reduction in amplitude of pulsations of the temporal artery was 52 per cent (figure 3). In one subject observations continued to be made at intervals during eighty minutes after injection, and the ergotamine effect was still maximal. Though no certain inferences about the diameter of an artery may be drawn from the amplitude of its pulsations, it is likely that decrease in amplitude associated with rise in blood pressure and decrease in heart rate represents local vasoconstriction.

Nevertheless, to determine directly whether ergotamine tartrate constricted the superficial temporal and occipital vessels, they were photographed during and after attacks under identical conditions. Figure 4 shows such photographs. In *A*, taken when the headache was maximal, the temporal artery stands out prominently. *B* was taken twenty minutes after ergotamine tartrate (0.4 mg.) had been given intravenously. It is apparent that the artery was less prominent. (A record of the changes in the amplitude of pulsations in this subject is shown in figure 1.) Likewise, direct observation in man on the middle meningeal artery (a branch of the external carotid artery) during a craniotomy revealed a decrease of approximately 20 per cent in the

diameter of the artery following the intravenous injection of 0.5 mg. of ergotamine tartrate.

B. *Relation of Headache to the Effects of Ergotamine Tartrate on Branches of the Internal Carotid Arteries.*—The amplitude of pulsations

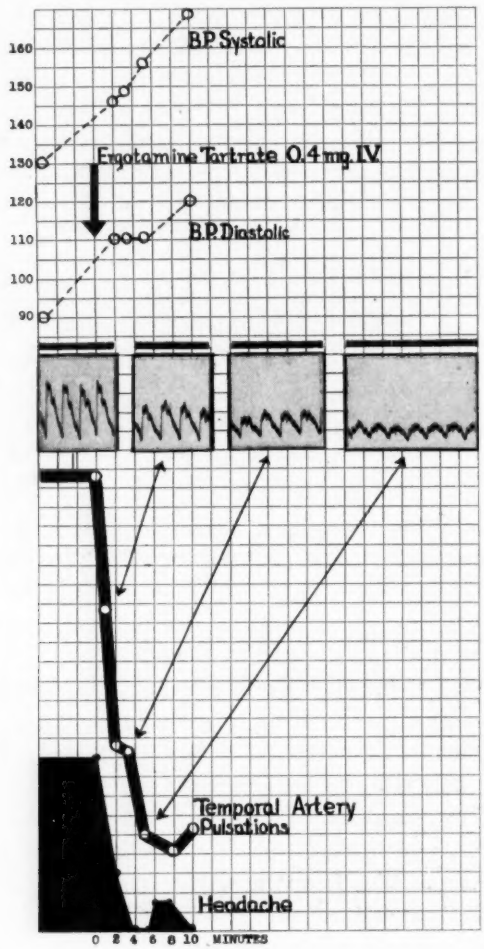


Fig. 1.—Relation of the amplitude of pulsations of the temporal artery to the intensity of headache after administration of ergotamine tartrate. The sharp decrease in the amplitude of pulsations following injection of ergotamine closely paralleled the rapid decrease in intensity of the headache. Representative sections of the photographic record are inserted. The average amplitude of pulsations for any given minute before and after administration of ergotamine was ascertained by measuring the individual pulsations from the photographic record. The points on the heavy black line represent these averages, expressed as percentages. In this record and those in the accompanying figures the initial or "control" amplitude was taken as 100 per cent. The interrupted line represents intervals of one second.

of the intracranial and intravertebral arteries, reflected in the cerebrospinal fluid, was observed in five patients during five attacks of migraine headache and their subsequent abolition. In two of these subjects, after injection of ergotamine, there was an initial decrease in the amplitude of pulsations, followed by an increase of a variable extent. In the

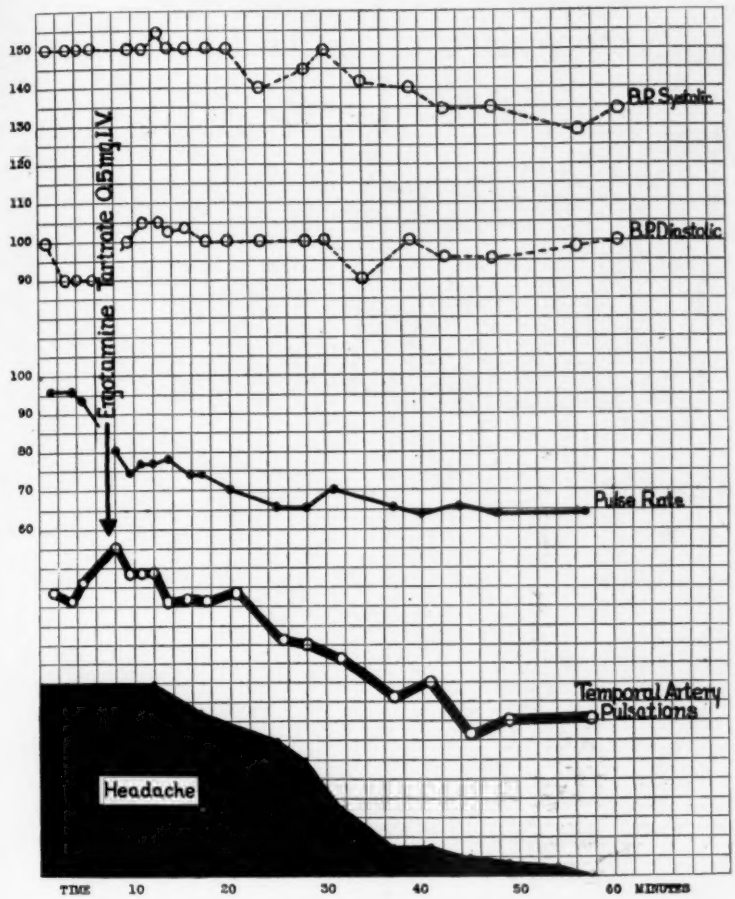


Fig. 2.—Relation of the amplitude of pulsations of the temporal artery to the intensity of headache after administration of ergotamine tartrate. Whereas in the patient whose record appears in figure 1 the headache terminated in ten minutes, in this subject it diminished gradually in intensity over the course of an hour. However, a similar parallelism existed between the state of the headache and the amplitude of pulsations, since the amplitude of pulsations also diminished slowly.

The points on the heavy black line represent the average amplitude of pulsations for the given minute, expressed in percentages.

other three subjects the initial decrease was not observed, and only an increase was evident. In no instance could a correlation be established between the amplitude of the pulsations and the state of the headache. Although the intensity of the headache steadily declined, the pulsations

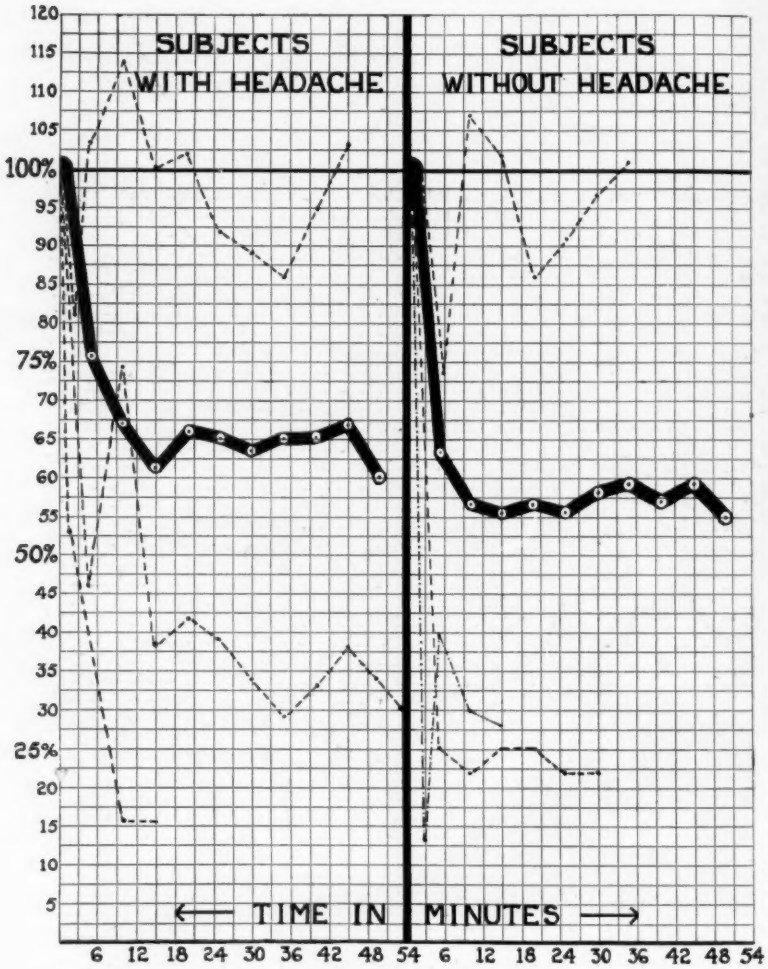


Fig. 3.—Effect of ergotamine tartrate on the amplitude of pulsations of the temporal and the occipital artery in twenty subjects with headache (fifteen and five, respectively) and on that of the temporal artery in thirty-four subjects without headache. The effect of ergotamine on the amplitude of pulsations in individual experiments was expressed in percentages of the amplitude during the preergotamine period and then averaged. The heavy black line in the diagram represents the average for all individual averages of the height of pulsations at five minute intervals after the administration of ergotamine tartrate. The dotted lines represent the extremes of individual variation, both above and below the average.

might be larger or smaller than during the control period. An example of this may be seen in figure 5, in which the changes in the amplitude of pulsations apparently bear no relation to the course of the headache.

In a series of twenty-eight subjects used as controls, the effect of ergotamine on pulsations of the cerebrospinal fluid was also observed to be inconstant. In eleven of these subjects the amplitude of pulsations initially decreased and subsequently increased, as in figure 13. In seventeen subjects the amplitude was variable and irregular (fig. 6). Thus, of thirty-three subjects with or without migraine headache, thirteen showed a decrease in the amplitude of pulsations followed by

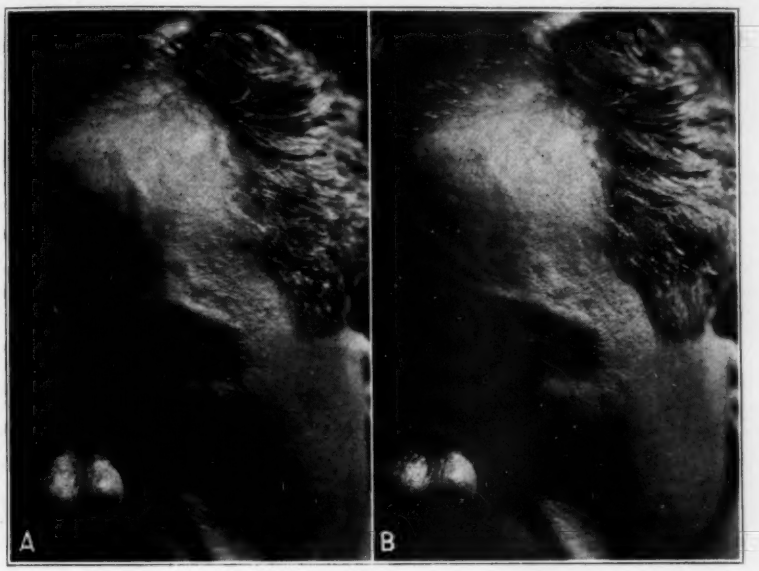


Fig. 4.—Appearance of the temporal artery before and after termination of migraine headache by ergotamine tartrate. Photograph *A* was taken while the patient was suffering from a left-sided migraine headache. The temporal arteries stood out clearly. Photograph *B* was taken under identical conditions twenty minutes later. In the interim the patient had received ergotamine tartrate (0.4 mg.) intravenously, and his headache had been abolished. The temporal vessels were then much less prominent. (In figure 1 is the record of the changes in the amplitude of pulsations of the temporal artery in this subject.)

a subsequent increase. In the remaining twenty subjects the ergotamine tartrate appeared to have a variable and inconstant effect.

To determine directly whether ergotamine tartrate exerted any appreciable influence on the branches of the internal carotid artery, photographs were taken of the retinal vessels before and after administration of this agent. In three such experiments no significant reduction

in the caliber of the arteries was observed, although the retinal veins became slightly narrower (fig. 7). Also, in the case of a woman with focal convulsions in whom a bone flap was elevated for purposes of exploration, the carefully exposed sylvian artery and its branches were

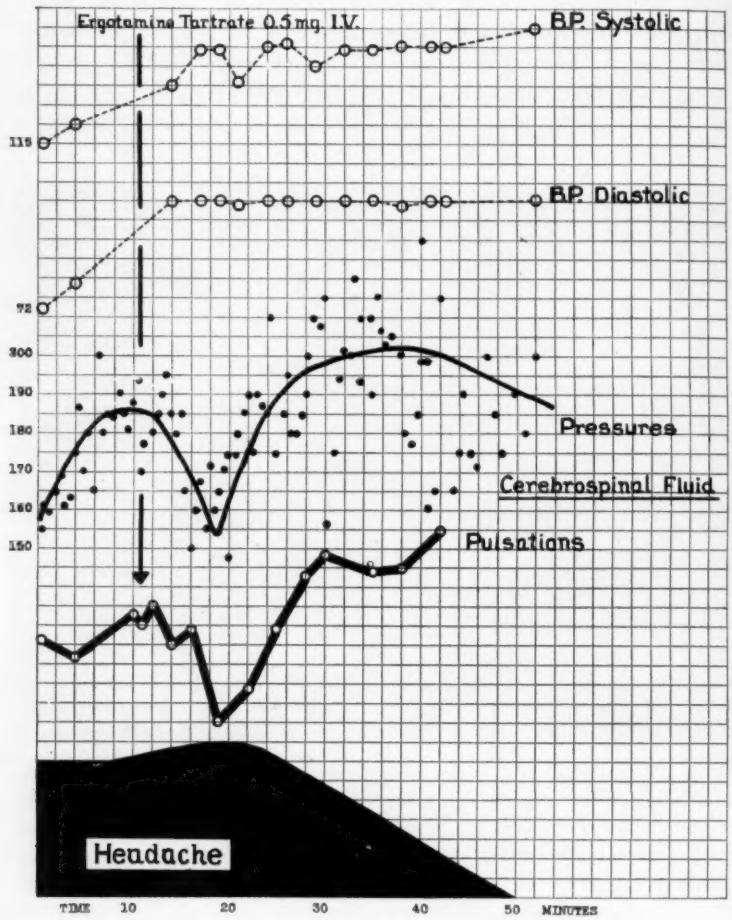


Fig. 5.—Relation of the amplitude of pulsations and pressure of the cerebrospinal fluid to the intensity of the headache during the action of ergotamine tartrate. The injection of ergotamine was followed at first by a decrease and then by a secondary increase in the amplitude of pulsations of the cerebrospinal fluid. These changes were not related in any consistent manner with the state of the headache. Similarly, the height of the cerebrospinal fluid pressure failed to bear any relation to the state of the headache. At the end of the experiment, when the headache had been abolished, the pressure was approximately the same as at the beginning, when the headache was severe.

The points on the heavy black line represent the average amplitude of pulsations for the given minute, expressed in percentages of the amplitude during the preergotamine period.

observed and photographed. Records were taken before and at five minute intervals for one hour after the intravenous injection of ergotamine tartrate. During the first twenty minutes after the injection there was no manipulation of the cortex, except for the repeated

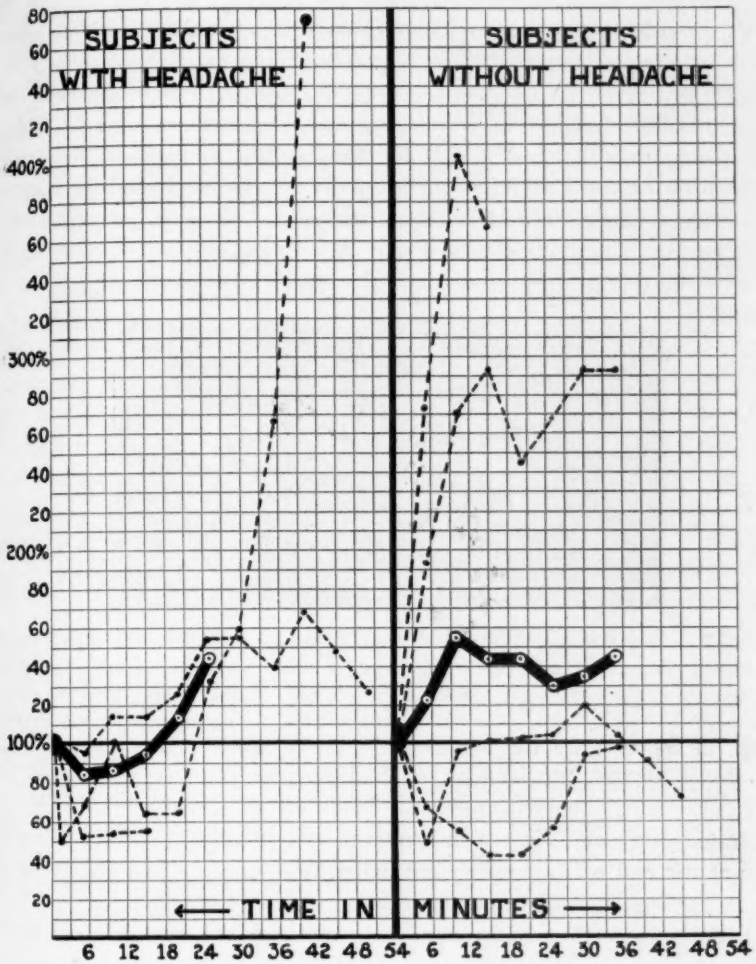


Fig. 6.—Effect of ergotamine tartrate on the amplitude of pulsations of the cerebrospinal fluid in five subjects with headache and in twenty-eight subjects without headache. The effect of ergotamine on the amplitude of pulsation in individual experiments was expressed in percentages of the amplitude during the preergotamine period and then averaged.

The heavy black lines represent the averages for all individual averages of the amplitude of pulsations of the cerebrospinal fluid determined at five minute intervals after the administration of ergotamine tartrate. The dash lines represent extremes of individual variation, both above and below the average.

dropping of warm saline solution to prevent surface dehydration. After this a small cortical scar, about 5 cm. from the artery, was removed. Only minimal, if any, constriction of the sylvian artery and its branches or of the large transcortical veins could be ascertained. The effect of ergotamine tartrate on the pial vessels of man as determined by direct observation is being further investigated.

C. *Effects of Ergotamine Tartrate on Cerebrospinal Fluid Pressure.*—Measurements were made of the cerebrospinal fluid pressure in four subjects during four attacks of migraine headache and their abolition. In three instances the pressure was between 130 and 160 mm. of saline solution during maximal headache. In none of the four subjects did the termination of the headache by means of ergotamine have any significant effect on the pressure. The average rise in pressure after the injection was about 20 per cent, but in no case was there correlation between the change in pressure and the state of the headache. This is

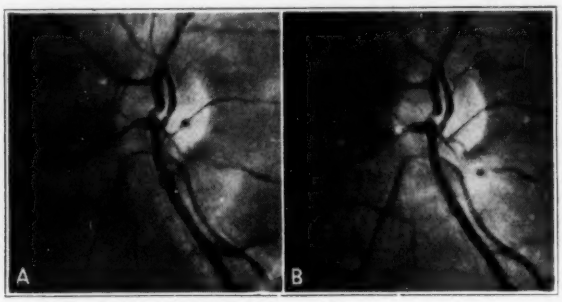


Fig. 7.—Appearance of the retinal arteries before and after the injection of ergotamine tartrate. Photograph *A* was taken before, and photograph *B* twenty minutes after, the intravenous injection of 0.5 mg. of ergotamine tartrate. The arteries of the retina, branches of the internal carotid artery, showed no appreciable change in caliber after the injection. The veins appeared slightly narrowed. (Dr. M. L. Berliner permitted use of the photographs.)

illustrated in figure 5, in which it may be seen that the pressure was the same at the end of the experiment, when the headache had ended, as it was at the beginning, when the headache was severe.

In a group of thirteen control subjects in whom pressure readings were recorded, similar results were obtained. There was an average rise of 25 per cent in the cerebrospinal fluid pressure after injection of ergotamine, but individual variability was marked.

D. *Effects of Ergotamine Tartrate on Blood Pressure, Pulse Rate, Pulsations of the Radial Artery and Skin Temperature.*—Blood Pressure: After the administration of ergotamine tartrate, the average rise in blood pressure in sixty subjects was about 20 per cent. There was no appreciable difference between the responses of the migraine group and those of the control group.

Pulse Rate: The average decline in the pulse rate in fifty-two patients was 18 per cent. Here, too, there was no significant difference between the responses of the two groups.

Pulsations of the Radial Artery: In ten of the control subjects records were made of the amplitude of pulsations of the radial artery by the method already described for the temporal artery. In this small group of subjects the amplitude of pulsations of the radial artery showed an average reduction of 38 per cent, as compared with a reduction of 42 per cent for the temporal artery.

Skin Temperature: In three patients with migraine and seven subjects without headache, the skin temperature of the ear and cheek showed a change of no more than 1 degree C. (1.8 degrees F.) (fig. 8). In one control subject the skin temperature of the hand rose 10 degrees C. (18 degrees F.).

Comment.—The slowing of the pulse (Lev and Hamburger[7]), the slight rise in the pressure of the blood and the cerebrospinal fluid and the state of the headache observed here are in accord with the findings of other investigators (von Storch and Merritt;[8] Pool, von Storch and Lennox[9]). The maintenance of the skin temperature at a fairly constant level, despite constriction of the arteries, may be attributed to a concomitant rise in the systemic arterial blood pressure sufficient to compensate for the local cutaneous vasoconstriction (Lennox, Gibbs and Gibbs;[10] Lennox and Leonhardt[11]). The elevation in the skin temperature of the hand in the instance mentioned was attributed to the apprehension of the subject at the onset of the experiment, which diminished as the experiment proceeded (Mittelmann and Wolff[12]).

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7. Lev, M. W., and Hamburger, W. W.: Studies in Thyroid Heart Disease: The Value of Ergotamine in Hyperthyroidism and Its Effect on the Electrocardiogram, Am. Heart J. **8**:134, 1932.

8. von Storch, T. J. C., and Merritt, H. H.: The Cerebrospinal Fluid During and Between Attacks of Migraine Headaches, Am. J. M. Sc. **190**:226, 1935.

9. Pool, J. L.; von Storch, T. J. C., and Lennox, W. G.: Effect of Ergotamine Tartrate on Pressure of Cerebrospinal Fluid and Blood During Migraine Headache, Arch. Int. Med. **57**:32 (Jan.) 1936.

10. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: Effect of Ergotamine Tartrate on the Cerebral Circulation of Man, J. Pharmacol. & Exper. Therap. **53**:113, 1935.

11. Lennox, W. G., and Leonhardt, H. C.: The Flow and Concentration of Blood as Influenced by Ergot Alkaloids and as Influencing Migraine, Ann. Int. Med. **11**:663, 1937.

12. Mittelmann, G., and Wolff, H. G.: Experimental Observations on Changes in Skin Temperature Associated with Induced Emotional States, Tr. Am. Neurol. A., to be published.

E. *Effects of Ergotamine on Perception and Reflex Activity.*—In no instance was the perception of touch, temperature or superficial or deep pain affected by ergotamine tartrate.

Dilatation of the pupil as the result of pinching the skin of the neck was apparently as readily obtained in ten subjects at the height of the ergotamine action as it was before this agent had been given.

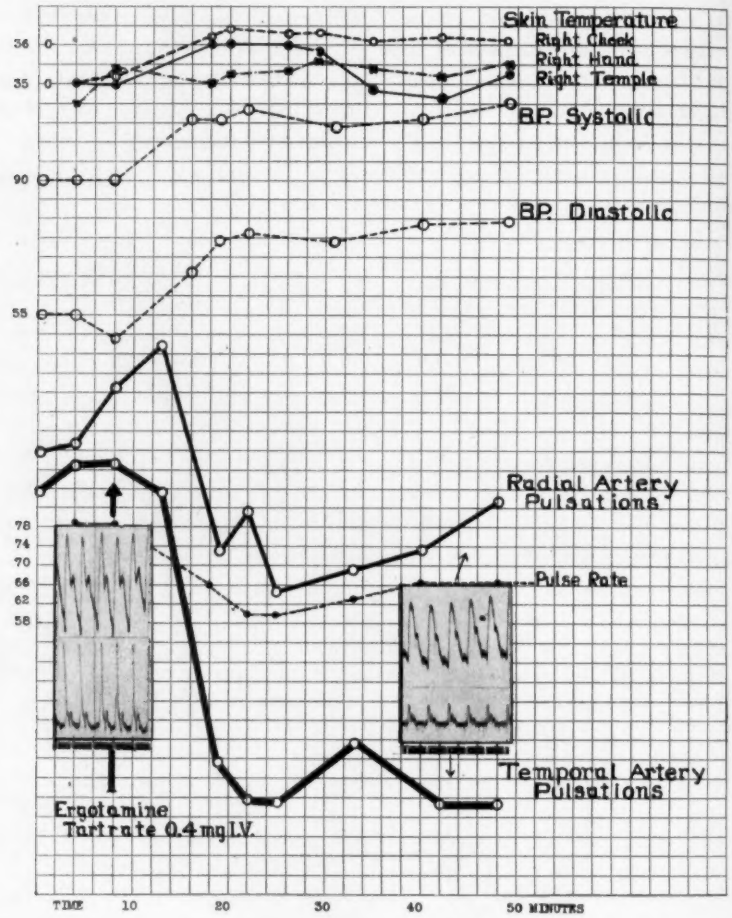

Fig. 8.—Effect of ergotamine tartrate on the amplitude of pulsations of the temporal and radial arteries, and on blood pressure, pulse rate and temperature of the skin of the cheek, temple and hand in a subject used as a control. Representative sections of the photographic record of the pulsations show the "initial" level and the decrease after the injection of ergotamine.

The points on the heavy black line represent the average amplitude of pulsations for the given minute, expressed in percentages. The interrupted line represents intervals of one second.

F. *Relation of Headache to Other Factors Affecting the Pulsations of Cranial Arteries.*—1. Effect of Manual Pressure on Arteries: Pressure was exerted with the thumb on the common carotid artery of the affected side during twenty-four attacks of migraine in ten subjects. In all instances the headache was alleviated while the pressure was exerted, and in many it was abolished. Pressure on the opposite common carotid artery afforded no relief. Furthermore, pressure on the temporal artery relieved the pain in the anterior half of the head, and pressure on the occipital artery relieved the pain in the posterior half. Several subjects stated that pressure on the temporal and occipital arteries relieved the pain on the affected side and "took a layer off the headache," but some pain persisted. This remnant of pain originated within the skull, since it was removed by obliteration of the common carotid artery on the side of the headache.

That all of the headache was not referred pain, and that the relief afforded in these experiments was not due to "counterirritation" from pressure applied indiscriminately to the painful zone, were demonstrated by the fact that it was necessary to press on the artery itself in order to diminish the pain.

These experiments are represented graphically in figures 9 and 10. In figure 9 pressure at *X*, over the temporal artery, temporarily abolished the pain in the area filled with small *x*'s, and similar pressure at *O*, over the occipital artery, temporarily abolished the pain in the area filled with *o*'s. Pressure at *OX*, over the common carotid artery, temporarily abolished the pain in both areas.

In figure 10 simultaneous tracings were taken of the pulsations of the two temporal arteries. The patient had headache only on the left side. Pressing on the right common carotid artery resulted in marked reduction in the amplitude of pulsations of the right temporal artery, but the headache on the left side was not affected. By pressure on the left common carotid artery, marked reduction in amplitude of pulsations of the left temporal artery resulted in distinct alleviation of the headache. Ergotamine tartrate was then injected, and the headache diminished in intensity and finally terminated as the pulsations decreased.

2. Effects of Epinephrine: Since migraine headache is occasionally diminished or abolished by epinephrine (Hunt;[13] Brock, O'Sullivan and Young[14]), the effects of this agent were studied. Five-tenths cubic centimeter of epinephrine hydrochloride (1:1,000) was administered subcutaneously to two subjects during attacks of migraine.

13. Hunt, T. C.: Bilious Migraine: Its Treatment with Bile Salt Preparations, Lancet **2**:279, 1933.

14. Brock, S.; O'Sullivan, M. E., and Young, D.: The Effect of Non-Sedative Drugs and Other Measures in Migraine, with Especial Reference to Ergotamine Tartrate, Am. J. M. Sc. **188**:253, 1934.

For a short period the headaches were diminished. In one instance the amplitude of pulsations of the cerebrospinal fluid increased as the headache improved after the injection. The record of the amplitude of pulsations of the temporal artery was technically unsatisfactory. However, in the other subject the amplitude of pulsations of the temporal artery was observed to decrease by 30 per cent during

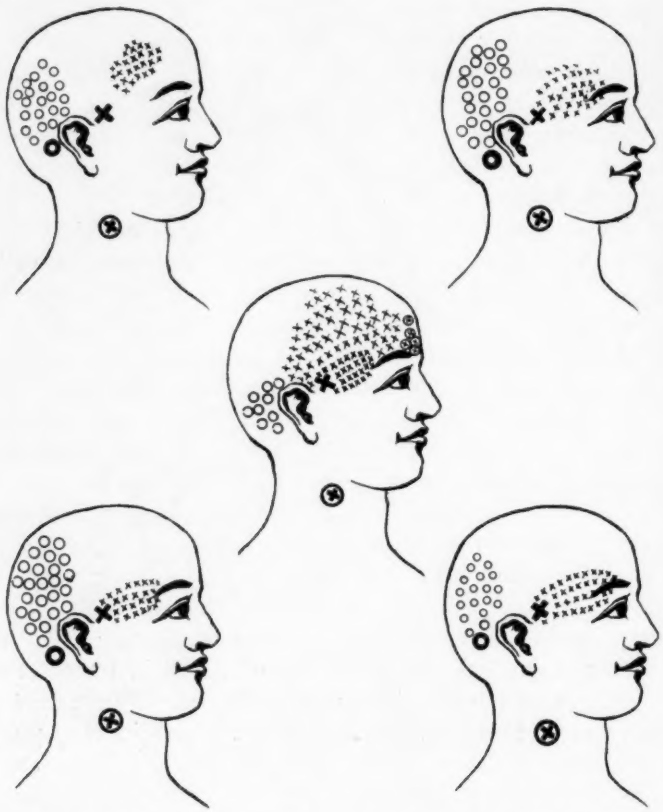

Fig. 9.—Relation of intensity of headache to changes in amplitude of pulsations produced by pressure on cranial arteries. In these diagrams the area of headache is designated by *x*'s or *o*'s. Obliteration of the temporal artery at *X* relieved headache in the areas covered by small *x*'s, and obliteration of the occipital artery at *O* relieved headache in the areas covered by small *o*'s. Pressure exerted on the carotid artery at *OX* relieved the headache entirely. In the central figure headache behind the ear and over the eye is represented by *ox*'s, to signify that it was not abolished by pressure on the occipital or the temporal artery, but only by pressure on the common carotid artery, at *OX*.

the temporary reduction in intensity of the headache (fig. 11). When the amplitude of pulsations returned to its original level the headache also returned. Ergotamine tartrate was then administered, and the headache

was abolished as the amplitude of pulsations was reduced 75 per cent for a prolonged period.

3. Effects of Histamine: Histamine phosphate was given intravenously to three subjects after attacks of migraine headache had been terminated by ergotamine and the amplitude of pulsations of the temporal arteries reduced. In each instance the histamine caused a sudden, temporary increase in the amplitude of pulsations, accompanied by a severe headache, which disappeared only as the amplitude

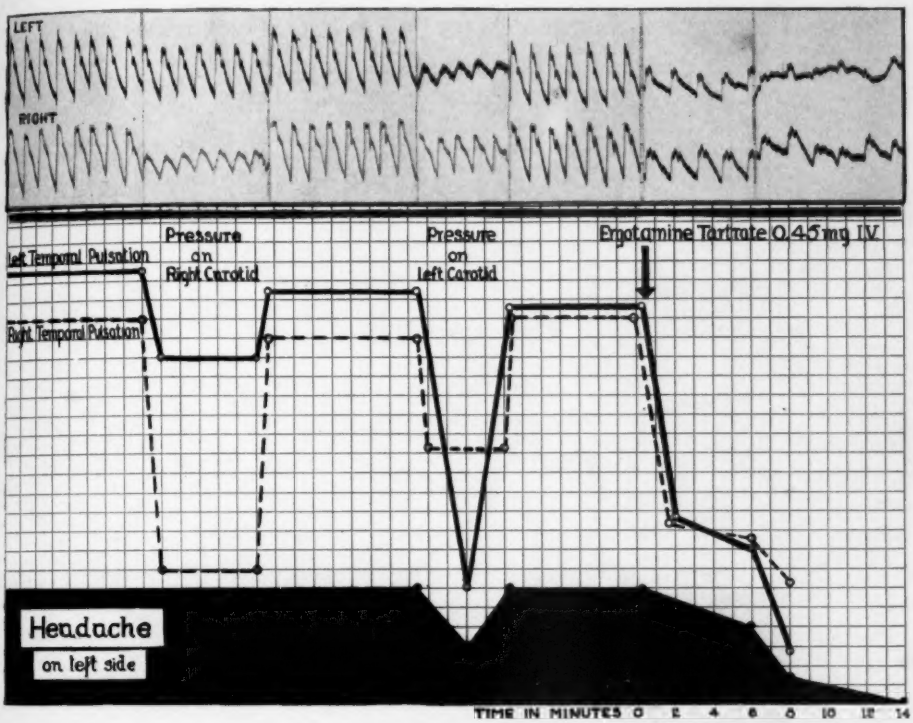

Fig. 10.—Relation of intensity of headache to changes in amplitude of pulsations of the temporal arteries during pressure on the common carotid artery of the affected and the unaffected side. Representative sections of the photographic record of the amplitude of pulsations of the left and right temporal arteries are shown at the top, with a diagrammatic representation of their amplitudes just below. Pressure on the right common carotid artery decreased the amplitude of pulsations of the right temporal artery, but did not affect the headache on the left side. Pressure on the left common carotid artery reduced the amplitude of pulsations of the left temporal artery and alleviated the headache on the same side. Finally, ergotamine tartrate was given, and the amplitude of pulsations and the intensity of headache diminished together.

The points on the heavy black lines represent the average amplitude of pulsations for any given minute, expressed in percentages. The interrupted line represents one second intervals.

of pulsations declined to the postergotamine level. Figure 12 is a record of one of these experiments. It will be noted that the curve for the amplitude of pulsations follows closely the curve for the intensity of headache, not only as the migraine headache was abolished but later, when the experimental headache was induced by histamine.

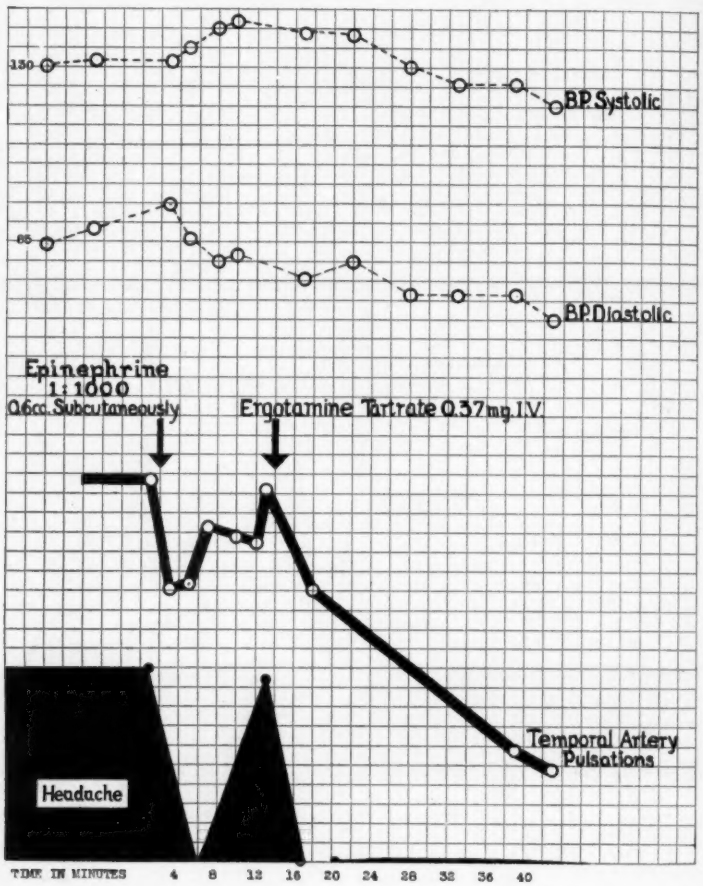

Fig. 11.—Relation of the intensity of headache to the amplitude of pulsations of the temporal artery after administration of epinephrine. After the injection of epinephrine the amplitude of pulsations of the temporal artery decreased by 30 per cent with simultaneous reduction in the intensity of the headache. When the amplitude of pulsations returned to the initial level the headache also returned. The administration of ergotamine tartrate was then followed by prolonged decrease in the amplitude of pulsations and termination of the headache.

The points on the heavy black line represent the average amplitude of pulsations for the given minute, expressed in percentages.

The capacity of histamine to break through the ergotamine effect and cause an increase in the amplitude of pulsations of the cranial arteries was also observed in thirteen control subjects. In each instance the increase in pulsations was accompanied by headache (fig. 13). In

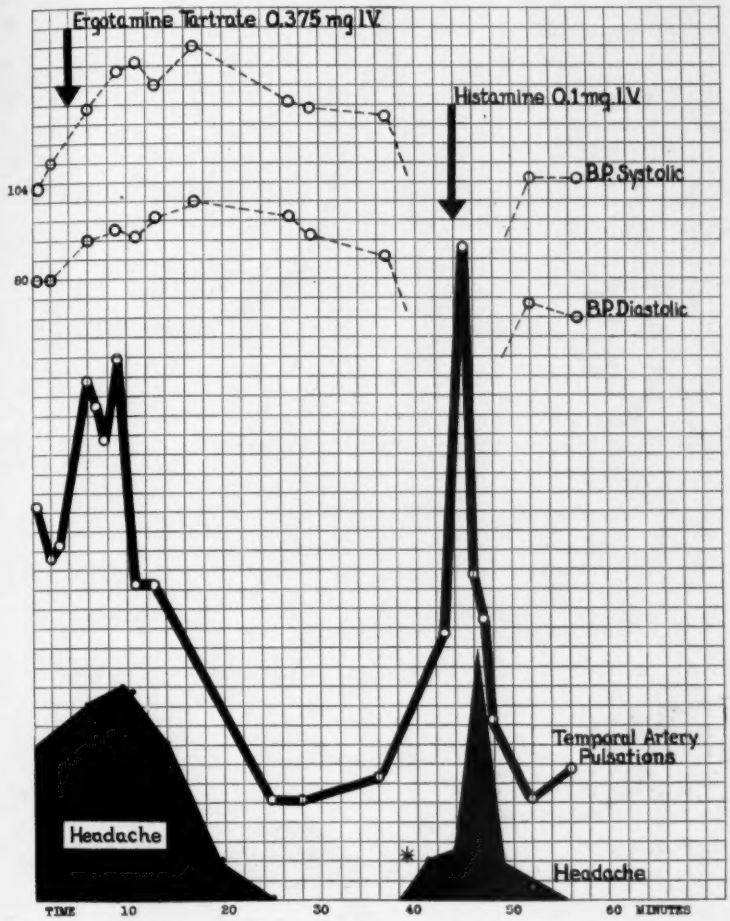

Fig. 12.—Relation of the amplitude of pulsations of the temporal artery to the intensity of migraine headache and headache induced by histamine. The amplitude of pulsations of the temporal artery and the intensity of the migraine headache declined simultaneously after the injection of ergotamine tartrate. At the point marked by the asterisk the patient was informed that she would receive another injection. Her apprehension was accompanied by a slight return of headache and increase in the amplitude of pulsations. The headache became severe when histamine was given, and the amplitude of pulsations increased sharply. The headache diminished as the amplitude of pulsations returned to the postergotamine level.

The points on the heavy black line represent the average amplitude of pulsations for the given minute, expressed in percentages.

all instances the amplitude of pulsations finally returned to the level at which it had been after the administration of ergotamine and before the injection of histamine. In eleven of these subjects observations were made on the amplitude of pulsations of the cerebrospinal fluid as

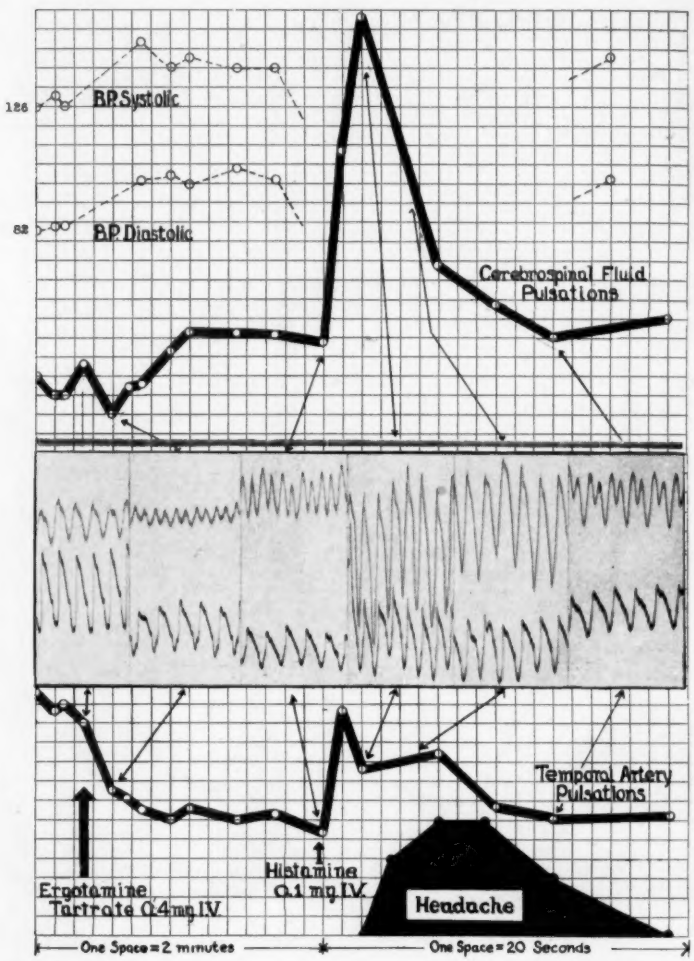

Fig. 13.—Effect of histamine on the amplitude of pulsations of the cerebrospinal fluid and of the temporal artery on a control subject who had previously received an injection of ergotamine tartrate. Representative sections of the photographic record are inserted. The points on the heavy black line represent the average amplitude of pulsations for the given minute, expressed in percentages. The interrupted line represents one second intervals.

well as of the temporal artery. Histamine caused an increase in amplitude of as much as 250 per cent in both instances.

One of the experiments of this series fortuitously brought forth an interesting correlation (fig. 14). The subject had a migraine headache on the left side. Tracings were taken of the pulsations of both the right and the left temporal artery. The headache was then terminated by ergotamine. Shortly thereafter, the patient was given half (0.05 mg.) of the usual amount of histamine phosphate used to induce headaches, and his headache returned, but only on the left side. Figure 14 reveals that the amplitude of pulsations of the temporal artery also increased only on the left side.

4. Effects of Distention of the Temporal Artery: In one subject in whom pressure on the temporal artery abolished the headache in the

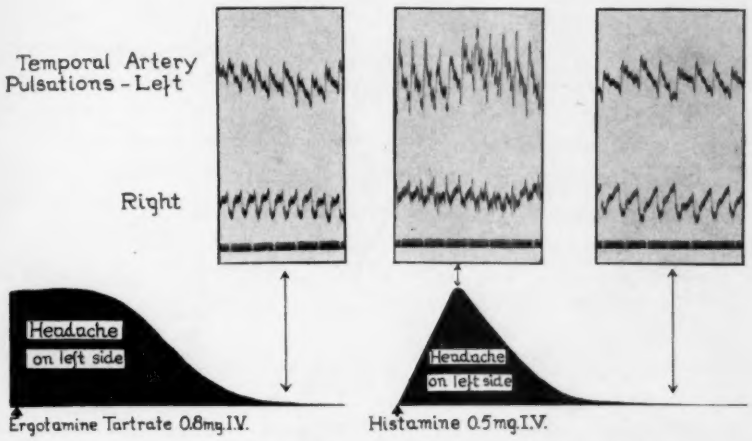

Fig. 14.—Relation of the amplitude of pulsations of the temporal artery to the intensity of a unilateral headache induced by histamine. A left-sided migraine headache was abolished by ergotamine tartrate. Half the dose of histamine phosphate usually required to produce histamine headache was injected. A headache of short duration, but only on the left side, resulted. Also, increase in the amplitude of pulsations occurred only on the left side. Representative sections of the photographic record are shown. The interrupted line represents one second intervals.

temporal region, periarterial infiltration of this vessel near its source with procaine hydrochloride was found to have the same effect. Therefore, ligation of the temporal artery was considered in this case for possible relief from the increasingly frequent attacks of headache (two and three times a week). As a preliminary step, a cannula with attached syringe containing physiologic solution of sodium chloride was tied into the artery in such a way that the afferent nerves about the vessel were not interrupted. The artery was then compressed about

1 inch (2.5 cm.) beyond this point. Sudden pressure applied to the plunger of the syringe caused the artery to be visibly distended. In each of several trials such distention was accompanied by severe pain referred to the temporal region. After this, the artery and surrounding nerve fibers were ligated and cut. This subject's headaches previously had extended over half his head, whereas in attacks which occurred

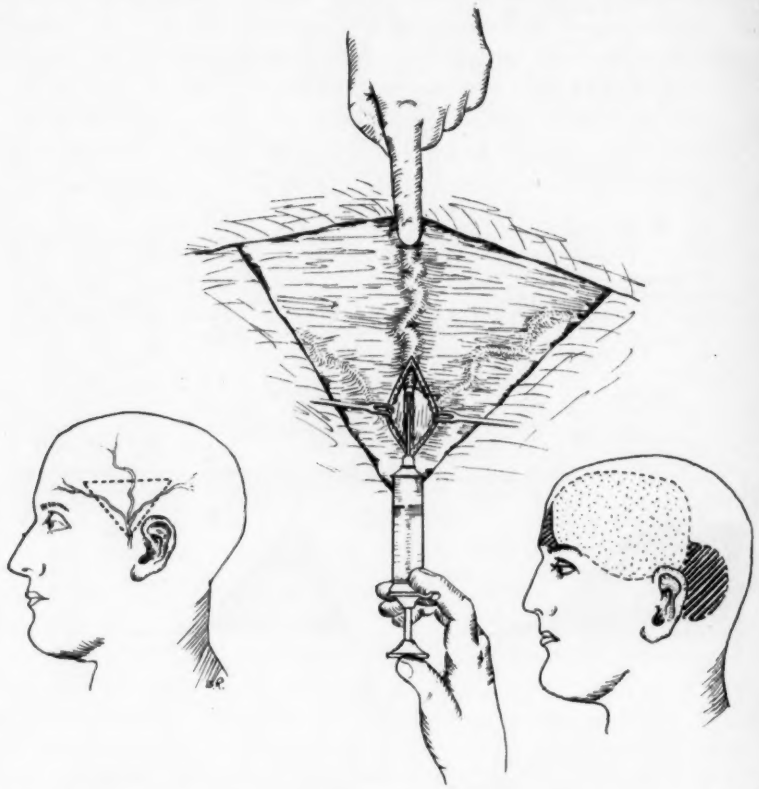

Fig. 15.—Head pain caused by distention of the temporal artery. A cannula and syringe were tied into the left temporal artery in such a manner as not to interrupt the afferent nerves about the vessel. The artery was compressed with the finger from 2.5 to 3 cm. beyond this point. Distention of the artery by increasing the intramural pressure through injection of saline solution was accompanied by pain. In attacks of migraine headache occurring on the left side subsequent to the ligation of the artery and nerves, pain was absent in the dotted area shown in the insert in the lower right corner. (Operation was performed by Dr. Bronson Ray.)

during two months after the operation the temporoparietal region was spared, the pain being present only behind the ear and in a small area over the medial aspect of the forehead (fig. 15).

G. *Veins.*—Though no exact measurements of the veins were made, it was observed repeatedly that prominence of the large veins, with increased visibility of the arteries, was a common accompaniment of migraine headache. The distended temporal and frontal veins were most apparent and, though visible when the patient was erect, were often particularly striking when the supine position was assumed. However, manual pressure applied directly to these veins or to the large cervical veins had no constant effect on the intensity of the headache. Some patients were relieved slightly by the maneuver; others were unaffected, and a few were made slightly more uncomfortable. Constriction of the arteries after administration of ergotamine tartrate was associated with narrowing of the veins.

COMMENT

In an attempt to evaluate these data, discussion will center about three questions: First, are cranial vessels potential sites of pain, and what variety of stimuli are pain producing? Second, does the headache of migraine arise from the cranial vessels? Third, what is the mode of action of ergotamine in terminating migraine headache?

Faradic stimulation of blood vessels of the meninges, both the dural and the larger pial vessels, gives rise to painful sensations (Levine and Wolff,[15] Penfield,[16] Fay[17]). Also as already shown, dilatation of the temporal arteries may give rise to head pain. The conclusion that cranial arteries are potential sites of pain may also be derived from an analysis of headache induced with histamine, since in this type the increased amplitude of pulsations of the cranial arteries is associated with headache. Relaxation of the walls of the blood vessels of the head through histamine does not in itself greatly increase the amplitude of pulsations or induce pain if there is at the same time a fall in systemic blood pressure. However, relaxation of the arterial walls plus average systemic blood pressure causes a great increase in the amplitude of pulsations of the cranial arteries and pain. Obliteration of the superficial arteries does not prevent the occurrence of headache following injection of histamine (Pickering[18]), thus indicating that intracranial as well as extracranial arteries participate in the production of this type

15. Levine, M., and Wolff, H. G.: Cerebral Circulation: Afferent Impulses from the Blood Vessels of the Pia, Arch. Neurol. & Psychiat. **28**:140 (July) 1932.

16. Penfield, W.: A Contribution to the Mechanism of Intracranial Pain, A. Research Nerv. & Ment. Dis., Proc. **15**:399, 1935.

17. Fay, T.: Mechanism of Headache, Tr. Am. Neurol. A. **62**:74, 1936.

18. Pickering, G. W.: Observations on the Mechanism of Headache Produced by Histamine, Clin. Sc. **1**:77, 1933.

of head pain. It therefore is reasonable to infer that increase in the stretch of dilated vessels, both extracranial and intracranial, may give rise to headache.

Implication of the cranial vessels in the attacks of migraine headache has often been suggested (see reviews by Riley [19] and Bassoe [20]). Such suggestions have arisen from several long-known facts; for example, the intensity of the headache during a migraine attack is diminished as long as the common carotid artery on the affected side is pressed on (Parry and Mollendorf, cited by Liveing; [21] Brunton [21a]). Moreover, the headache is found to diminish in intensity locally when the particular artery which supplies the affected region is pressed on (Hare [22]). Also, striking dilatation of the temporal arteries and veins may often be seen during the attack of migraine headache (Cushing [23]).

The experiments of this study confirmed these observations. The temporal and occipital arteries were investigated intensively, not because it was inferred that these arteries alone are involved in the production of pain but because they are large and representative branches of the external carotid artery, and for technical convenience. However, it is probably significant that the areas of the head in the vicinity of these two arteries and their branches are commonly the sites of pain in migraine. Moreover, in four subjects in this series the migraine headache could be abolished completely by mechanical obliteration of the temporal and occipital arteries, suggesting that, at least in some subjects, the major portion of the pain arises from the superficial branches of the external carotid artery.

The relation between the amplitude of pulsations and the headache induced experimentally by histamine has already been cited. It seems likely from these studies that there is an analogous relation between the amplitude of pulsations and headache in the migraine attack. Thus, the amplitude of pulsations of the superficial branches of the external carotid artery closely parallels the intensity of the headache, and reduction in the intensity of the headache is intimately associated with decrease in the amplitude of pulsations. In fact, the headache ended when the amplitude of pulsations of these arteries was sufficiently

19. Riley, H. A.: Migraine, Bull. Neurol. Inst. New York **2**:429, 1932.

20. Bassoe, P.: Migraine, J. A. M. A. **101**:599 (Aug. 19) 1933.

21. Liveing, E.: On Megrim, Sick Headache and Some Allied Disorders, London, J. & A. Churchill, 1873.

21a. Brunton, T. Lauder: On Disorders of Digestion, Their Consequences and Treatment, London, Macmillan & Co., 1886, pp. 103 and 104.

22. Hare, F.: Mechanism of the Pain in Migraine, M. Press & Circ. **1**:583, 1905.

23. Cushing, H.: The Special Field of Neurological Surgery: Five Years Later, Cleveland M. J. **9**:827, 1910.

decreased, whether by means of ergotamine, epinephrine or pressure. The converse was also true; namely, headache, once terminated by the vasoconstrictor action of ergotamine, was brought back by the vasodilator action of histamine and the accompanying increase in amplitude of pulsations. The properties of these four agents differ widely; yet they have in common a capacity to alter the amplitude of pulsations of cranial arteries. It is reasonable to postulate that their ability to induce headache or alter its state is dependent on the one property which they possess in common.

Any doubt concerning the vasoconstrictor action of ergotamine tartrate on the branches of the external carotid artery was resolved by the direct observations on and photographs of the middle meningeal and temporal arteries, both before and after the injection. Such an effect was to be anticipated, because on direct observation in cats it was found that ergotamine regularly constricted arteries of the dura and skin by an average of 25 and 39 per cent, respectively (Pool and Nason [24]).

Some older observations concerning the middle meningeal artery are relevant to this discussion. It has been noted that attacks of migraine headache often fail to recur after subtemporal decompression (Cushing [23] and Gordon Holmes [25]). Since such a procedure customarily includes ligation of branches or the trunk of the middle meningeal artery, the suggestion presents itself that this artery plays a part in the production of pain. There is also more direct evidence that the middle meningeal artery is implicated, since ligation of this vessel abolished attacks of migraine headache in some subjects (Dickerson [26]). In others, however, this procedure diminished the intensity, but did not prevent the recurrence of attacks.

There are further indications that the middle meningeal branch of the external carotid artery is a source of pain in an attack of migraine. Faradic stimulation and traction on the external carotid artery near its source give rise to a boring pain, usually felt deep in or behind the eye (Fay [17]). When the middle meningeal artery is stimulated or irritated farther from its source, the resultant pain is localized in the temporal region (Fay,[17] Craig [27]). Pain back of the eye during an

24. Pool, J. L., and Nason, G. I.: Cerebral Circulation: XXXV. The Comparative Effect of Ergotamine Tartrate on the Arteries in the Pia, Dura, and Skin of Cats, Arch. Neurol. & Psychiat. **33**:276 (Feb.) 1935.

25. Holmes, Gordon, cited by Critchley, M., and Ferguson, F. R.: Migraine, Lancet **1**:182, 1933.

26. Dickerson, D. G.: The Surgical Relief of the Headache of Migraine, J. Nerv. & Ment. Dis. **77**:42, 1933.

27. Craig, W. M.: Localized Headache Associated with Lesion of Meningeal Vessels, J. A. M. A. **100**:816 (March 18) 1933.

attack of migraine headache is common. Moreover, in instances in which the headache is incompletely abolished by pressure on both the occipital and the temporal artery, the residual pain seems to arise usually from behind or within the eye, as well as from the temporal region. It is conceivable that this pain arises, at least in part, from the immediate environs of the middle meningeal artery.

The role of the internal carotid arteries in the attack of migraine headache and the effect of ergotamine on these arteries remain to be determined with certainty. . The methods employed here are not completely satisfactory for their study, and the data may not be accepted as proof that the large basal vessels are not implicated in the attack or influenced by ergotamine tartrate. Although in these experiments the amplitude of pulsations of the cerebrospinal fluid bore no consistent relation to the state of the headache, it is conceivable that major changes may have taken place in isolated branches of the internal carotid arteries and have been obscured by the reactions of the rest of the intracranial and intraspinal arterial tree. Ergotamine tartrate caused the pial vessels in cats to react variably, and direct observation in man revealed no appreciable constriction in the retinal or pial arteries. Nevertheless, until the basal vessels can be observed more directly, no conclusions should be drawn concerning the role of the branches of these arteries in the headache of migraine.

Since branches of both the internal and the external carotid arteries appear subcutaneously and on the dura, it would be arbitrary to contrast these vessels too sharply.

Phylogenetically (Tandler [28]), the ophthalmic and middle meningeal arteries are intimately related. In the insectivora, for instance, both arteries have a common stem in the stapedius artery. Furthermore, in Otaria jubata (sea-lion) the ophthalmic artery actually springs from the internal maxillary artery (i. e., a branch of the external carotid artery). Even in the apes the middle meningeal artery has a good-sized connection with the ophthalmic artery, whereas the connection with the internal maxillary artery is still weakly developed. In man this connection with the internal maxillary artery predominates, but the anastomosis with the ophthalmic artery persists, even though it is feeble. This relationship in man is further indicated in the occurrence of a variety of anomalies. Thus, the ophthalmic artery may spring from the middle meningeal artery, or, inversely, the middle meningeal artery may arise from the ophthalmic artery. In one instance reported the ophthalmic artery arose from the internal carotid artery on one side and from the middle meningeal artery on the other.

Although the branches of the external carotid artery predominate numerically, both superficially and on the dura, it must be remembered that the anterior meningeal artery arises from the anterior ethmoid artery, which in turn comes from the ophthalmic branch of the internal carotid

28. Tandler, Julius: Zur vergleichenden Anatomie der Kopfarterien bei den Mammalia, Vienna, C. Gerold's Sohn, 1898.

artery. Furthermore, the supra-orbital and frontal arteries, both superficially and on the forehead, also arise from the ophthalmic artery. Therefore, it is possible that the migraine headache referred to the middle of the forehead, back of the nose or behind the eye may also involve branches of the ophthalmic artery, i. e., branches of the internal carotid artery.

That the cranial veins play no important part in producing the headache is likely from the evidence adduced. Though these veins were dilated there was no evidence of venous stasis, since an appreciable rise in intracranial venous pressure would have shown itself in elevation of the cerebrospinal fluid pressure. No such rise was found. Moreover, interference with the cranial venous outflow by manual pressure on the great cervical veins had no constant effect on the intensity of the headache.

When the mode of action of ergotamine tartrate in abolishing the migraine headache is considered, it is evident at once that the effect is not that of an analgesic, since the threshold for pain in general and for headache specifically is not elevated (Lennox, von Storch and Solomon [29]). Indeed, intense headache can be induced by histamine at a time when the effect of ergotamine is maximal. Explanation of the headache-ending effect must lie elsewhere.

It has long been known (Dale [30]) that preparations of ergot in relatively large amounts diminish the responses of smooth muscle to epinephrine and adrenergic nerve stimulation. It was emphasized early, however, that ergot derivatives are used in the clinic in amounts so small that they could not produce the aforementioned paralytic effects. Nevertheless, it was on the basis of such effects that ergotamine was introduced into the therapy of migraine. It was assumed that the attack of migraine headache resulted from spasm of the cranial arteries following excessive autonomic nerve excitation and that the ergotamine caused relaxation of these blood vessels (Tzanck [1]). Such an explanation of the headache-terminating action of ergotamine must also be discarded, since it is easy to demonstrate that responses via the cranial sympathetic pathways, such as dilatation of the pupils on pinching the skin of the neck, are not disturbed by the amounts of ergotamine that terminate severe headache. Moreover, there is no evidence that the migraine headache is the result of vasospasm. Certainly, ergotamine caused no relaxation of the walls of cranial blood vessels in these experiments.

A far more likely explanation of the mode of action of ergotamine tartrate in ending attacks of migraine headache can be derived from

29. Lennox, W. G.; von Storch, T. J. C., and Solomon, P.: Effect of Ergotamine Tartrate on Non-Migrainous Headaches, Am. J. M. Sc. **192**:57, 1936.

30. Dale, H. H.: On Some Physiological Actions of Ergot, J. Physiol. **34**:163, 1906.

the evidence presented here. The capacity of relatively small amounts of ergot preparations to contract rather than to dilate the smooth muscle of arterial walls has been established. Such vasoconstriction occurs even in the absence of vasomotor nerves (von Storch [31]). Moreover, the repeatedly observed parallelism between the state of the cranial arteries and the intensity of the headache makes it likely that this relationship is not fortuitous. In short, the most acceptable explanation of the headache-ending effect is that cranial arterial walls which are painfully stretched and dilated are caused to narrow through the vasoconstrictor action of ergot.

SUMMARY AND CONCLUSIONS

1. Changes in the intensity of migraine headache were found to be related closely to changes in the amplitude of pulsations of certain branches of the external carotid arteries. Factors that decreased the amplitude of pulsations decreased the intensity of headache and vice versa.

2. Reduction in the amplitude of pulsations of the temporal artery by manual pressure on the common carotid artery of the affected side was accompanied by reduction in the intensity of the migraine headache. In some subjects the headache was temporarily abolished by pressure on the temporal and occipital arteries alone. In others a residuum of deep pain persisted after obliteration of these superficial cranial arteries.

3. Distention of the temporal artery by increasing experimentally the intramural hydrostatic pressure resulted in pain.

4. Ergotamine tartrate, in diminishing the intensity of migraine headache, reduced the amplitude of pulsations of the aforementioned arteries by approximately 50 per cent. When the intensity of the headache diminished rapidly the amplitude of pulsations likewise decreased rapidly, and when the intensity of the headache lessened slowly the pulsations decreased slowly. Observations and photographic records were made during thirty-two attacks of migraine in sixteen subjects.

5. Observations and photographs made before and during the action of ergotamine revealed vasoconstriction of the temporal and middle meningeal arteries. To this may be attributed the previously described reduction in the amplitude of pulsations.

6. The data permitted no definite inferences concerning the state of the internal carotid arteries and their branches during the attack of migraine headache or the reaction of these vessels to ergotamine during its abolition.

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31. von Storch, T. J. C.: Personal communication to the authors.

7. The threshold for the perception of pain, both superficial and deep, as well as that of headache induced by histamine, was not appreciably elevated by ergotamine tartrate. Moreover, the response of smooth muscle to sympathetic nerve stimulation was not perceptibly diminished by the intravenous injection of 0.5 mg. of ergotamine tartrate.

8. These data lend support to the postulate that the head pain of the migraine attack is produced by the distention of cranial arteries and that termination of the headache by ergotamine tartrate is due to the capacity of this agent to constrict these cranial arteries and thus reduce the amplitude of their pulsations.

RESTLESSNESS IN CHILDREN

PAUL M. LEVIN, M.D.
DALLAS, TEXAS

This study began with the observation of a boy aged 11 years, who was seen because of epileptic attacks. During the examination the patient was almost constantly in motion, darting about the room and handling most of the available objects for a few moments each. His attention could be held for only very short periods. An older sister, who had brought him, told of his excessive appetite. His breakfast, for example, usually consisted of four large bowls of cooked cereal with milk and sugar, six slices of buttered bread and a cup of coffee with milk and sugar. In spite of this intake of food, the boy had always appeared mildly undernourished. His intelligence quotient, as determined by the Stanford revision of the Binet-Simon test, was 54. The combination of restlessness, morbid hunger and mental defect recalled the behavior of animals in which experimental lesions have been made in the prefrontal region of both frontal lobes. A plan was then formulated to study a series of restless children, to determine how often cerebral lesions can be demonstrated and what evidence there is of such lesions involving the frontal lobes of the cerebral hemispheres.

REVIEW OF LITERATURE

Restless overactivity in monkeys with lesions of the frontal lobe was first described by Ferrier,[1] in 1876. He noted states of apathy alternating with restless and purposeless wandering, and called attention to an inhibitory-motor function of the frontal lobe. Bianchi[2] confirmed this finding and described other changes in behavior after this lesion. More recently, Jacobsen[3] and Richter and Hines[4] have also demonstrated an increase in motor activity after bilateral ablation

From the Subdepartment of Neurology of the Johns Hopkins University.

1. Ferrier, D.: The Functions of the Brain, New York, G. P. Putnam's Sons, 1876.

2. Bianchi, L.: The Mechanism of the Brain and the Function of the Frontal Lobes, translated by J. H. MacDonald, New York, William Wood & Company, 1922.

3. Jacobsen, C. F.: A Study of Cerebral Function in Learning: The Frontal Lobes, J. Comp. Neurol. **52**:272, 1931.

4. Richter, C. P., and Hines, Marion: To be published.

of the prefrontal region (particularly area 9 of Brodmann). Fulton, Jacobsen and Kennard [5] noted that these animals have also an increased appetite.

Clinical observers, too, have described motor overactivity in patients with lesions of the nervous system, particularly in early life, in the senile period and in toxic states. The disorders are all characterized by prominence of mental symptoms. An excellent summary of the motor abnormalities associated with mental deficiency has been presented by Tredgold.[6] Excessive activity may occur with all degrees of intellectual defect, the character of movement varying in general with the mental capacity. In idiots the movements are usually simple stereotypies, such as continuous rocking of the chair or turning of the head from side to side. Imbeciles show more complex activity, often manifested as constant chattering and running about. In morons the movements are more purposeful, although equally restless; habit spasms may be frequent. Attention is generally poor in all types. Not all mental defectives show this overactivity; many are placid and industrious.

In adults, restlessness occurs particularly in certain cases of senile degeneration or diffuse arteriosclerotic disease of the cerebral cortex, in intoxication (delirium) and occasionally in dementia paralytica. The presenting symptom in these cases is disturbance of mentation. Thus, as Critchley [7] pointed out in his review of the neurologic changes in old age, restlessness is a "physical concomitant of senile dementia rather than of pure senility." The pathologic alterations in cases in which mental disturbances are prominent are widely distributed over the cerebral cortex but are most marked in the frontal lobes. In the case in which the most extensive prefrontal ablation on record was carried out, Brickner [8] described pronounced motor unrest associated with mental defects. Morbid hunger is frequently associated with such restlessness, at all ages; it has been noted in cases of tumor, particularly of the frontal lobe, as well as in association with developmental defect, senile and presenile cortical degeneration, arteriosclerotic disease of the brain and dementia paralytica.[9]

5. Fulton, J. F.; Jacobsen, C. F., and Kennard, Margaret, A.: A Note Concerning the Relation of the Frontal Lobes to Posture and Forced Grasping in Monkeys, Brain **55**:524, 1932.

6. Tredgold, A. F.: Mental Deficiency (Amentia), ed. 5, New York, William Wood & Company, 1929.

7. Critchley, M.: The Neurology of Old Age, Lancet **1**:1119 (May 23); 1221 (June 6); 1331 (June 20) 1931.

8. Brickner, R. M.: The Intellectual Functions of the Frontal Lobes, New York, The Macmillan Company, 1936.

9. Fulton, J. F.: Some Functions of the Cerebral Cortex: I. Autonomic Representation in the Cerebral Cortex, J. Michigan M. Soc. **33**:175, 1934. Watts, J. W.: The Relation of the Frontal Lobes to Visceral Function, M. Ann. District of Columbia **4**:99, 1935.

MATERIAL

Case histories from the Harriet Lane Home outpatient clinics for epilepsy and child psychiatry were reviewed.[10] Two hundred and seventy-nine cases in which diurnal restlessness was a prominent symptom were selected. The ages of the patients ranged from 3 to 15 years. The cases were subjected to analysis which included data on birth and development, history of previous cerebral disease, occurrence of convulsive attacks, environmental disturbances, abnormal neurologic findings and intellectual standardization. Instances in which the restlessness was probably due to hyperthyroidism or chorea were excluded, as were also cases of simple tic, habit spasm and nocturnal restlessness. The degree of overactivity was roughly graded as "marked," "moderate" or "mild." The distinction was made between restlessness at home, as related in the history, and that manifest during the visits to the clinic. This distinction tends to illustrate the influence of two factors: the degree of control over somatic activity which the children possessed and the influence of disturbing elements in the home environment. A consecutive series of 273 nonrestless children serving as controls were analyzed with regard to intellectual status.

The complaint of restlessness was generally expressed as: "The child can't sit still," "is always on the go" or "is all over the place." Three fourths of the children showed this incessant activity during their visits to the clinic. The type of activity varied from fidgetiness to wild, purposeless behavior. Most of the children ran about the room, inspecting and handling all objects of any interest, without settling down to play with any one thing. They often chattered constantly. Distractability was marked, but it did not seem to be an adequate explanation of the overactivity. The movements themselves were excessive, aimless and frequently stereotyped. Furthermore, the restlessness was often poorly controlled by the full effort of the patients. These features suggest that the inhibitory powers of the patients were not adequate to control the motor activity.

PRESENTATION OF DATA

The intelligence ratings of the 279 restless children were compared with those of the control group of 273 nonrestless children (fig. 1). The curves for the incidence of the various intelligence quotients in these groups showed definite impairment of intellectual capacity in the restless children.

The children with overactivity were then arranged in three groups: those whose behavior was characterized by marked restlessness at all times, 92, those with moderate or mild restlessness, 115, and those who were restless at home but on their visits to the clinic showed normal psychomotor activity, 72. Frequency curves for the intelligence quotients in these groups showed clearly a relation between the degree of restlessness and the severity of the intellectual defect (fig. 2). The markedly restless children gave considerably lower per-

10. Drs. E. A. Park and Leo Kanner, of the Harriet Lane Home, gave permission to use the records of their clinics, and Miss Mary McCulloch, social worker, aided in the study of the cases.

formances than did the others. The children who were restless only at home had intelligence ratings approximately equal to (or perhaps slightly higher than) those of the normal control group.

The differences between the various groups of children were indicated by the averages of the intelligence quotients. The average rating for the entire restless group was 80, and that for the nonrestless group was 92. Of the restless group the markedly overactive children had

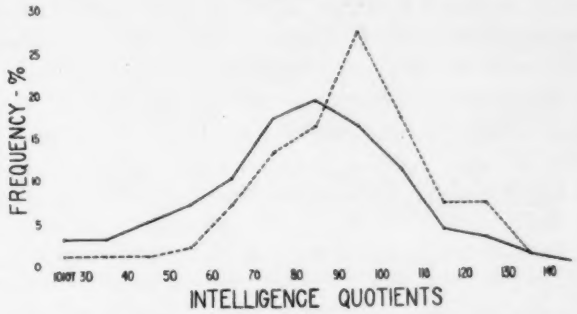

Fig. 1.—Curves for incidence of intellectual levels in the group of 279 restless children (solid line) and the group of 273 nonrestless children (broken line).

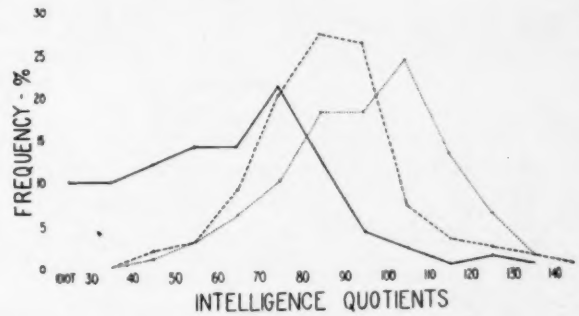

Fig. 2.—Curves for incidence of intellectual levels in 92 cases of marked restlessness (solid line), 115 cases of moderate and mild restlessness (broken line) and 72 cases in which the restlessless was readily controlled (dotted line).

an average rating of 62, and the moderately and mildly overactive, one of 86. The average intelligence quotient for the group who were restless only at home was 95. It may be inferred, then, that restlessness that cannot be controlled is associated with reduction in performance of intelligence tests. This intellectual inferiority may in part be merely apparent, since highly restless children would be less cooperative in the performance of the tests. Much of this difficulty, however, can be overcome by patience on the part of the examiners.

The data were analyzed in a somewhat different way, as summarized in the accompanying table. The cases in the three groups described were divided into: (1) those in which definite evidence of a cerebral lesion was presented, such as cerebral trauma at or after birth, lethargic encephalitis, infantile cerebral palsy, repeated convulsions, spastic paralysis and microcephaly; (2) those in which there was only retardation of cerebral maturation, as indicated by slowness in walking (after 18 months of age) or in talking (after 3 years of age), regardless of the intellectual status; (3) those in which only subnormal intelligence (intelligence quotient below 85) was presented, and (4) those in which there was no evidence of cerebral disease.

The incidence of cerebral disease was as follows: congenital defects of the brain, manifested by cerebral paralysis of prenatal origin or microcephaly, 17 cases; serious birth trauma, 4 cases; definite postnatal injury to the head followed by appearance of cerebral symptoms, 13

Evidence of Cerebral Lesions in 279 Restless Children

Degrees of Restlessness	Number of Children	Definite Disease of the Brain		Slow Development		Subnormal Intelligence (I. Q. Below 85)		No Evidence of Lesion	
		No.	%	No.	%	No.	%	No.	%
Marked	92	69	75	8	9	13	14	2	2
Moderate and mild	115	39	34	11	10	29	25	36	31
Evident only at home	72	17	24	2	3	12	16	41	57
Total	279	125	46	21	8	54	19	79	29

cases; cerebral degeneration associated with icterus gravis neonatorum, 1 case; lethargic encephalitis, 4 cases; congenital neurosyphilis, 4 cases; lead encephalopathy, 7 cases; infantile cerebral paralysis, 14 cases, in 1 of which the disease was associated with a facial nevus, and conditions in which epilepsy was present but the nature of the cerebral lesion was not apparent, 61 cases.

Analysis of the data presented in the table indicates that the highly restless children presented much more frequent evidence of cerebral lesions than did the children in the other groups. A gradation in the incidence of cerebral disease was evident in the highly restless, mildly restless and nonrestless groups of children. Conversely, cases in which there was no tangible cerebral disorder became more frequent as the restlessness decreased, suggesting that overactivity in otherwise normal children is more subject to control than it is in children with cerebral disease.

Forty-four of the patients had morbid hunger in addition to restlessness. The voracity did not appear to be merely appetite improved by the excessive somatic activity, as many highly restless children had

normal or even poor appetites and also as several children were observed who had morbid hunger with normal motor activity. The overactivity was marked in 30 of the cases of morbid hunger, mild or moderate in 4 and easily controlled in 4. The average of the intelligence quotients was 66. Analysis in these cases showed that excessive appetite ranked with marked restlessness in association with mental deficiency and structural defects of the brain.

COMMENT

Structural Defects of the Brain.—Cerebral lesions are responsible in large part for the production of severe forms of restlessness, as is evident from the data presented. The pathologic types of cerebral disorder include practically all diseases of the forebrain common in children.

Cerebral agenesis is a common member of this group. In cases of mental deficiency Hammarberg,[11] Bolton[12] and Tredgold[6] demonstrated an immature condition of the cerebral cortex, which is as a rule most severe in the frontal region. This retarded maturation, the probable cause of delay in such functions as walking and talking, likewise seems to be the basis for the delay in control over motor activity.

The overactivity often bore a definite relation to convulsive seizures, either as a transient postconvulsive symptom or as a lasting sequel. In severe epilepsy restlessness may change into the opposite state of torpor and decrease in activity, return to overactivity being then effected by appropriate anticonvulsive therapy.

Psychologic Disturbances.—These appeared to be important in the production of mild forms of restlessness. Thus, of 79 children with normal or superior intelligence who gave no evidence of cerebral disease, the restlessness was mild in all but 3, and in 40 it was not apparent in the behavior at the clinic. The psychiatric records in these cases showed that 35 children had been badly spoiled, 32 came of highly emotional and delinquent families and 14 had difficulties in school. These environmental disturbances were of two types—faulty training and conflict. Faulty training results from overindulgence or neglect. Children reared under these circumstances are deprived of the normal incentive for the utilization of their restraining powers and are apt to show motor overactivity. Environmental conflict may arise from such situations as cruel treatment or failure of achievement, such as failure at school because of reading disability. Overactivity appearing under these conditions reminds one of the extreme restlessness and general

11. Hammarberg, C.: Studien über Klinik und Pathologie der Idiotie, Upsala, E. Berling, 1895.

12. Bolton, J. S.: The Brain in Health and Disease, London, Edward Arnold, 1914.

excitability ("experimental neurosis") that Pavlov [13] observed in some dogs under the influence of antagonistic processes. These psychologic factors in restlessness, important as they are in organically sound children, are of at least equal importance in children with cerebral defects. When cerebral inhibition is already weakened from disease of the brain, mild degrees of environmental disturbance suffice to evoke clinical manifestations of defective control.

It should be emphasized that a complaint of restlessness is often made, particularly by oversolicitous parents, concerning a bright child who shows merely exuberance of spirit. The child is active because of a wide and eager interest in his surroundings. The activity in these cases is better directed along a unified course than it is in those of truly pathologic motor overactivity.

CONCLUSIONS

Marked restlessness and morbid hunger are associated in man with mental deficiency. In these cases there is a high incidence of cerebral lesions. The prominence of the mental deficiency suggests that the lesions, while often diffuse, may be most severe in the frontal lobes. The syndrome of restlessness, morbid hunger and mental deficiency appears to be directly comparable with the "syndrome of the prefrontal region" experimentally produced in primates and other animals.

Excessive motor activity occurs also without mental deficiency or demonstrable disease of the brain, the activity being more readily subject to control. Psychologic disturbances appear to be responsible for the restlessness in these cases.

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13. Pavlov, I. P.: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex, translated by G. V. Anrep, London, Oxford University Press, 1927.

BAD TASTE (CACOGEUSIA)

HENRY HARPER HART, M.D.
NEW YORK

In a review of the symptomatology of 1,000 psychiatric patients at the Vanderbilt Psychiatric Clinic a few years ago, I found a symptom the significance of which was not apparent to me—that of bad taste in the mouth. I was surprised to find that it was recorded in only 20 cases—in all of which the patients were women. The sexual monopoly seems in itself curious and leads naturally to certain psychoanalytic interpretations.

Psychoanalysts are familiar with the symbolic substitution of the mouth for the vagina, which occurs not only in dreams but in reality. The erotic significance of all the body orifices is generally accepted by freudian analysts, and the polymorphous perverse pleasures of the infant gain distorted expression in the neurotic adult. One sees clearly in fellatio the interchangeability of the mouth and the vagina.

There are other associations which connect this symptom with sexuality. Outstanding is the sense of smell. It is known to most psychologists that the sense of smell is more complex and differentiated than that of taste. Actually one finds only four pure taste sensations, but the variety of experiences of differentiated olfactory sensations is almost unlimited. Because of the close proximity of gustatory and olfactory sense organs and the more elaborate organization of the latter, it is natural that persons refer to taste when they are actually referring to smell. The sense of smell serves a variety of vital functions in lower animals, not the least of which is the sexual and reproductive function. Krafft-Ebing declared that in beasts the influence of olfactory perception in the sexual sense is unmistakable. He described the incapacity of young puppies to recognize the females when the olfactory nerves were extirpated. Henning, according to Brill, called attention to the direct transition from the olfactory gyrus to the gyrus fornicatus. Brill,[1] in an article published under the following title, "The Sense of Smell in the Neuroses and Psychoses," confirmed still more strongly the observations of others, such as Fliess and Ellis, on the psychologic association between olfactory and sexual functions. In some of Brill's cases the olfactory symptoms were not regarded as of primary importance, but in others the satisfaction and compulsion

1. Brill, A. A.: The Sense of Smell in the Neuroses and Psychoses, Psychoanalyt. Quart. **1**:7, 1932.

were of fetishistic significance. Because of the aforementioned association, it seemed of importance from the psychologic angle to explore a little into the psychosexual lives of the 20 patients who suffered from bad taste.

It was found that 9 of the women were married; 2 were divorced; 4 were widowed and the other 5 were unmarried. Unfortunately, in only 13 of the 20 cases were there records of adequately studied sex life. The accompanying table summarizes the data available.

Here, then, are 13 women, ranging in age from 21 to 51 years, all of whom complained of disagreeable taste in the mouth and also of sexual maladjustments, with the possible exception of D. K., who gave no information on her sexual life beyond a few casual remarks. This negative response might, on later investigation, prove to be the reverse. In all these cases there were definite aversion to the sexual rôle and rejection, expressed verbally or hysterically, in the form of vomiting or other symptoms. In several instances impotence, infidelity, desertion or brutality on the part of the husband were blamed for the lack of sexual gratification. In others, as in B. C., the conflict seemed to be more deeply rooted. All these women were sufficiently neurotic to come to a psychiatric clinic, where, except in the case of A. F., who was suffering from schizophrenia, the diagnosis of one or another form of neurosis was made. It is to be noted that rejection of the sexual rôle was the common factor in all these cases. How many of them had indulged in oral perversion of the sexual act, such as fellatio or cunnilinguism, was not ascertained. In the case of A. F., fellatio was probably practiced, but the data are lacking for the other patients.

Only 2 of the patients (A. F. and D. A.) presented cacogeusia as the chief complaint. In both these women disagreeable taste in the mouth was accompanied by unmistakable rejection of the sexual act. A. F. declared that she often awoke in the middle of the night with a bad taste in her mouth. She described it as sour or bitter. Her mouth felt dry. The taste was so bad "she felt she was going to die." She even dreamed about the disagreeable taste and awoke with it. She declared that for ten or twelve years she had had the bad taste every night. The symptoms were also associated with a lump in the throat and the sensation of choking. This patient had probably practiced oral perversion. In the case of D. A., the complaint spontaneously offered was coupled with the complaint of frigidity and the desire to be separated from her husband, whom she felt to be uncouth and overdemanding sexually.

One does not need to be a psychoanalyst to adduce instances of symbolic relationship between the mouth and emotional attitudes. The

literature is filled with colloquialisms and idioms referable to the mouth or, more particularly, to taste. When one is disgusted by something, one frequently says it causes "a bad taste in the mouth." One speaks of persons turning sour or bitter—two qualities of taste. Even the term "sweet" has been brought to represent anything pleasant. When disappointed, one depreciates the object of frustrated desire and says that "the grapes are sour." A lover will sometimes use this oral and gustatory expression in admiration of his beloved, by declaring her "sweet enough to eat." In this way, one might find in taste a symbolic expression of the state of the libido. Depressed and suicidal patients, engrossed with the desire to die, refuse food and reject the incorporative functions of life. It seems plausible, therefore, to conclude that disturbance in taste might denote disturbance in the erotic satisfaction of the person in question.

One may well ask why, of a total 1,000 patients with psychiatric conditions, most of whom probably suffered from some sexual maladjustment, these 20 women should complain of the symptom of bad or disagreeable taste. Probably if the other patients had been asked pointedly about the presence of this symptom, more positive replies would have been recorded. Does the symptom of cacogeusia represent any greater degree of sexual maladjustment than some other symptom —for example, dyspareunia? Is there some special factor which determines that sexual frigidity—a very common symptom, estimated by some to involve nearly 50 per cent of women—should express itself in an oral fashion? Before lending oneself to a predominantly psychologic point of view, one may ask what other factors of a physical nature may have possible determining significance.

When a patient complains of bad taste in the mouth, the step that most naturally occurs to the average physician is to look at the mouth. Since smell is confused with taste, the nasal passages may come second. Review of the records of these 20 patients shows that in 50 per cent there was definite evidence of dental infection or of some pathologic process involving the teeth or gums at the time of the complaint. In only 3 of the remaining half of the patients was dental infection definitely ruled out. In 1 of these patients dental infection was suspected, but there was no record of further examination or treatment. Five of the patients were considered to be so strikingly psychoneurotic that no physical examination was recorded, and whether dental or nasal infection occurred in these cases one cannot tell. Hence I can summarize the dental situation by listing dental infection in 10 patients, a doubtful condition in 7 and no infection in 3. However, since 2 of the 3 patients in whom dental infection was ruled out suffered from sinusitis or infection of the nasal passages, this leaves only

Data on Twenty Women with Psychiatric Disturbances Who Suffered from Cacogeusia

Name	Age, Years	Dental Infection	Pelvic Disease	Infections of Ear, Nose and Throat	Married or Single	Attitude Toward Sex	Taste	Other Physical Complaints
C. H.	55	.....	Cystocele and rectocele; senile uterus	Sinusitis	Married; husband alive; 8 children	?	Salty taste; pasty sensation and taste in eating	Varicose veins; hemorrhoids
D. A.	36	?	?	?	Divorced; deserted by husband	Complained of brutality and excessive sexual demands of husband; far happier without him; never had pleasure from coitus	Bad taste in the mouth; bitter taste	Arthritis
I. B.	39	Dental caries	Abortion; otherwise normal	?	Married; dominated her husband and brought him from a negligent to an attentive state	Occasionally permitted coitus, but no pleasure from it	Bad taste in the mouth	.....
F. C.	42	Many teeth removed	Cystocele and rectocele; chronic cervicitis; laceration of cervix; relaxed pelvic floor	Hypertrophic rhinitis; infected tonsils	Married; husband impotent; marital life unhappy; husband poor provider	Disgusted at husband's excessive sexual desire; later frustrated due to husband's impotence	"Bad taste" in the mouth	Arthritis; dermatophytosis; obesity
B. C.	28	?	Vulvar pruritus; pelvic operation	?	Single; disliked boys; wished for immaculate conception; dreaded marriage	"Nice people don't indulge in such hideous things"; said she "tolerated" men; was crazy about women's beauty; no homosexuality	"Sour taste in the mouth"	.....
D. K.	33	Dental infection; 7 rotten stumps of teeth	?	Tonsillar infection	Married 15 years; 4 children	Declared herself well adjusted to her husband	"Copper taste" in the morning	Appendectomy and operation on gallbladder; obesity
T. M.	37	Dental caries	Three miscarriages	?	Married at 23; neglected by husband, who is 8 years older, and German; patient is Jewish; suspected husband of infidelity	Constant fear of pregnancy; decline in sexual satisfaction in recent years	Bad taste in the mouth	None
F. G.	47	Dental infection	Abortion; hysterectomy at 45	Tonsillar enlargement	Husband weak; has epileptic seizures; does not support her	Felt better when her husband was in the hospital; apparently no enjoyment of coitus	Bad taste in the mouth	Hernia; varicose veins; cardiac disorder
L. F.	46	Dental caries	Foul-smelling vaginal discharge; some tears after first childbirth	Acute rhinitis or otitis media	Married at 20 to a man 18 years older; husband became bankrupt and jealous; died 8 years previously	Found sex repugnant; denied husband coitus; separated from him for year prior to his death	Bad taste in the mouth	Flat feet; visceroptosis; hemorrhoids; secondary anemia
C. M.	51	Dental caries	?	Normal	Married twice; second marriage after 10 years of widowhood	Never enjoyed coitus during second marriage; was never pregnant	Bad taste in the mouth in the morning	Visceroptosis

				Normal	Married twice; second marriage after 10 years of widowhood	Never enjoyed coitus during second marriage; was never pregnant	Bad taste in the mouth in the morning	Visceroptosis
A. F.	40	Dental caries	Fibroid of uterus	Normal	Husband 17 years older, died 4 years after marriage; paid little attention to her; "he was cold and dead"	Coitus always painful; feared to take chance with other men; "they were seldom any good"; had perverted sex relations with Italian gangster	Bad taste in mouth; "sweet and bitter"	Chronic conjunctivitis
R. A.	42	Pyorrhea alveolaris	Abortion; laceration of cervix; slight prolapse; purulent discharge	Normal	Married at 18; three spoiled children; feared her husband went with other women; tyrannized over him with her neurosis	Never enjoyed coitus; always afraid of pregnancy	Marked sourness in the mouth	None
A. F.	21	?	?	?	Single; always a woman's girl; vomited during menstruation	Never took boys seriously; no love affair; "I am cold and have no feeling of love at all"; disliked petting; no sex experience	Sickly taste, like some dead animal	?
A. F.	34	Many teeth removed for pyorrhea	Uterus drawn to left; otherwise normal	Normal	Married at 30; divorced at 32; thought her husband married her for money; husband was unfaithful, got another woman pregnant and disappeared	Could not submit to coitus because of husband's promiscuity; never any pleasure from coitus; husband often drank	"Brassy taste" in the mouth always	Goiter; spinal lordoscoliosis
D. H.	54	?	Pelvic operation	Infected tonsils; chronic sinusitis	Husband dead	?	Bitter taste in the mouth	General arteriosclerosis; hypertension; secondary anemia
M. O.	50	?	Pelvic operation	?	Divorced; sex life not investigated	Not ascertained	Bad taste in mouth	Osteo-arthritis; cystitis
M. P.	43	Teeth removed	?	Normal	Single; had been engaged to a sickly male nurse, who lost his position whenever they planned marriage; man died 2 years ago	Disrupted love affairs; frustrated sexual excitement; menopause	Bad taste in mouth (marked fetor oris)	Disease of skin; healed pulmonary tuberculosis; scoliosis of spine
D. H.	9	Dental infection	Gonorrhea	Chronic tonsillitis; adenoids	?	Gonorrheal vaginitis; sex life not investigated	Bad taste in mouth, with tingling on lips after grand mal seizures	Pes planus; pharyngitis; idiopathic epilepsy; disorder of skin
S. C.	29	Dental caries	?	Normal	Single (?)	Prudishness; refused to talk about her private life (?)	Sour taste in the mouth	Secondary anemia
F. G.	39	Pyorrhea	Prolapse of pelvis; laceration of cervix; retrocele; cystocele; chronic endocervicitis	Normal	?	Menopause (?)	Bad taste	Flat feet; varicose veins; umbilical hernia

1 of the 20 patients who could be regarded as free from nasal or oral infection. In reviewing the records in 1,000 random cases of psychiatric conditions, I found that dental infection is mentioned in only 15 per cent. This, of course, does not mean that in the other 85 per cent the teeth were normal. It refers only to examination and recording. However, if one takes the incidence of dental infection in the 20 cases as 80 per cent, one is apt to think of dental infection as being more than a mere chance factor.

This led me to estimate the incidence of disturbance in taste as described subjectively by patients with definite oral infection in the dental clinic. Through the department of dentistry, I was permitted to question 100 patients with oral infection about this symptom, as they were examined by the dentist. This series of patients included those with peridontoclasia, caries, gingivitis, stomatitis and other forms of oral sepsis. In response to my question whether they had ever noted disagreeable taste in the mouth, 54 per cent replied in the affirmative and 46 per cent in the negative. In the positive responses degrees of disagreeableness were estimated subjectively, as follows:

	Percentage
Marked	23
Fairly marked	9
Slight	18
Rare	4
Total	54

Curiously, of the entire group of 100 patients taken in order of admission to the dental clinic, 46 per cent were men and 54 per cent women. Of the 54 patients who definitely complained of dysgeusia 32, or 59 per cent, were women, while of the 46 patients who had never complained of any disagreeable taste 24, or 52 per cent, were men. This seems to suggest a slightly greater degree of sensitiveness to taste on the part of women than of men. There seemed to be no general relationship between the degree of dental caries or oral sepsis and that of dysgeusia. Some of the patients showed extreme degrees of pyorrhea, caries or apical infection—all without having noticed any change whatever—while others with merely one or two cavities were positive about the complaint of bad taste. The expressions used by these 100 dental patients were of interest. Eight of the 54 described the taste merely as "bad"; 12 used the expression "sour"; 17 called it bitter, salty or brackish, and 3, metallic. Other expressions recorded were "funny," "like decayed food," "mattery," "gassy," "nasty," "flat" and "disagreeable."

Other physical factors demonstrated at one time or another by the 20 women with cacogeusia are listed as follows, in order of the numerical incidence:

	No. of Cases
Pelvic disease or history of pelvic operation	9
Tonsillar enlargement or infection	4
Varicose veins	3
Pulmonary disorders	3
Malnutrition	3
Disorders of the skin	3
Pes planus	2
Spinal disorders—scoliosis, etc.	2
Secondary anemia	2
Hemorrhoids	2
Arthritis	2
Cardiac disorders	1
Hernia	1
Gonorrhea	1
Thyroid disorder	1
Chronic otitis media	1
Visceroptosis	1
Disease of the gallbladder	1
Obesity	1
Arteriosclerosis	1
Sinusitis	1
Nasal disorders	1

The high incidence of some form of pelvic disease or of the history of pelvic operation in these 20 women was remarkable: 9 of 20, or 45 per cent—almost as many as the patients with oral sepsis. Of the 1,000 random cases of psychiatric disturbance, there was a record of pelvic disorder in nearly 10 per cent. Does this higher incidence of pelvic disorder in the patients suffering from "bad taste" afford new confirmatory support to the aforementioned symbolic interpretation? Four of the 9 patients with pelvic disorder had dental infection as well, and 2 had infection of the tonsils. That, in addition to pelvic disorders, 6 of the 9 had an oral or nasal infection demonstrated the multiplicity of factors that seem to underlie this complaint.

Inquiry was made as to the incidence of this symptom in association with pelvic disease. Through the gynecologic department at the Vanderbilt Clinic, it was possible to study 44 random cases of pelvic disorder in females, ranging in age from 13 to 51. The pelvic conditions were described as: fibroid of the uterus, cystocele, ovarian cyst, hydrosalpinx, retroversion, endocervicitis, chronic cervicitis, polyp, chronic pelvic inflammation, gonorrheal salpingitis, pruritus vulvi, postabortive infection, rectocele, etc. Many of these conditions were found in combination in the same woman.

Of the 44 women with pelvic disease, only 15 answered negatively when asked if they had experienced a bad or disagreeable taste in the mouth. The question was asked at the time when the teeth were inspected, so as to avoid any suggestion of association with the pelvic disorder. Sixteen of the 44 women declared that the taste in the mouth was markedly disagreeable, while 29 in all had noted the complaint. When one sees that nearly two thirds of this group had noticed the symptom, one is less uncertain of a possible connection between pelvic and oral complaints. At the same time, the oral condition of these women was noted, and it was found that 21 of the 29 women with bad taste showed various degrees of oral sepsis, while of the 15 patients without disturbance in taste, oral sepsis was found in only 3, or 20 per cent. This seems to point to the importance of oral sepsis as a conditioning factor in determining disturbance in taste in women with pelvic disease. Unfortunately, it was not convenient at the time to undertake a serious study of the state of sexual satisfaction in these 44 women.

A survey of the other symptoms complained of by the 20 women with psychiatric disturbance associated with cacogeusia indicates that the disagreeable sensation is only one feature of a general neurotic picture and not something isolated or accentuated, except in the 2 cases previously mentioned. It may be of interest to list the other complaints in the series of 20 women.

Debility	13	Palpitation	6	Irritability	4
Constipation	12	Depression	6	Nocturia	4
Headache	12	Frequency of urination	6	Diarrhea	3
Abdominal pain	10	Pain in extremities	6	Tremulousness	3
Vomiting	9	Restlessness	5	Cough	3
Anorexia	9	Tinnitus	5	Dyspepsia	3
Hot and cold feelings	9	Vertigo	5	Fear of death	3
Backache	9	Nausea	5	Precordial pain	3
Ocular symptoms	7	Paresthesia	5	Faint spells	3
Emotional instability	6	Eructation	4	Pruritus	3
Diffuse pains	6			Dysphasia	2

Of some importance, perhaps, is the fact that associated with the complaint of disagreeable taste are four symptoms which accompany gastro-intestinal disorders. Constipation stands above all, with an incidence of 60 per cent in this group. This and the other gastro-intestinal symptoms are familiar in the story of the neurotic patient. Scarcely any neurotic patient is entirely free from them. However, in none of these 20 patients did peptic ulcer occur, and the only gastro-intestinal disorders recorded in the group were: hernia, in 1; visceroptosis, in 2, and infection of the gallbladder, in 1. In only 5 of the patients was roentgenographic study made of the gastro-intestinal tract, and the only significant findings were: enteroptosis, in 2, and slight colonic spasm, in 1. No evidence of serious organic disease of the alimentary tract was found.

Though it is natural to attribute disturbance in taste to a functional disorder of the alimentary tract, the symptom evidently is not considered to be important or frequent, for Morgan, in his work entitled "Functional Disorders of the Gastro-Intestinal Tract" (Philadelphia, J. B. Lippincott Company, 1931), mentioned only the possibility that abnormality in the digestive processes might result from hypergeusia or ageusia—by which is meant change in the acuteness of taste perception. He did not describe any cases in which disagreeable or peculiar taste sensations occurred as a prominent symptom or in which functional disturbance in taste led to functional digestive disturbance.

It is not my purpose in this paper to discuss all the factors that could have possible relevance in the causation of bad taste. Many other factors—chemical, neurologic and otolaryngologic—can be cited as causative, and the patients I have studied have not been subject to investigation of all these factors. Enough physical factors have been presented to show their importance in the 20 cases with disagreeable taste; the relevant importance, however, of the psychic factors of marital and sexual frustration and rejection has not hitherto been stressed, and the incidence appears to be too high to be ignored.

SUMMARY AND CONCLUSIONS

1. Cacogeusia, or foul, disagreeable taste in the mouth, is a symptom apparently more commonly complained of in women than in men.

2. The 20 women in this series, all of whom were psychiatric patients whose sex life was studied to some extent, showed frigidity or rejection of sexual pleasure and satisfaction.

3. Dental infection, oral sepsis or nasal infection could be excluded in only 1 of the 20 cases.

4. A high proportion (45 per cent) of these patients had had some form of pelvic disease.

5. Two thirds of a group of women with pelvic disease complained of bad taste in the mouth.

6. Fifty-four per cent of 100 patients with dental infection complained of this symptom.

7. In the 2 cases in which bad taste was a leading symptom, rejection of sexuality was unmistakable.

8. It seems safe to conclude that many women, particularly when suffering from dental, nasal or pelvic disorder, may complain of pronouncedly disagreeable taste in the mouth when their sex life is frustrated and void of any pleasure. In this way, accentuation of this symptom may give an additional symptomatic indication of the rejection of sexual life.

HUMAN AUTONOMIC PHARMACOLOGY

XI. EFFECT OF BENZEDRINE SULFATE ON THE ARGYLL ROBERTSON PUPIL

ABRAHAM MYERSON, M.D.
AND
WILLIAM THAU, M.D.
BOSTON

In the course of a study of the pharmacologic reactions of the human eye,[1] which was conducted as a part of the series of studies on human autonomic pharmacology, our attention became directed to the autonomic pharmacology of the Argyll Roberston pupil. One of us (A. M.) had observed that in the case of a patient who had tabes dorsalis and was under treatment for an anxiety neurosis of independent nature benzedrine sulfate, administered in doses of 20 mg. per day, gradually dilated the pupils and brought about a condition in which there was a partial reaction to light.

This formed the starting-point of a series of researches on the Argyll Robertson pupil,[2] of which this paper is a preliminary communication. Argyll Robertson himself defined the pupil which now forms a landmark in medicine as having four essential factors: (1) the pupil is small; (2) there is absence of the light reflex; (3) there is persistence of the convergence accommodation reflex, and (4) the reaction to instillation of atropine into the eye is delayed or only partial, while that to physostigmine (Càlabar bean) is normal. His conception of the pathologic physiology has been reformulated by Uriarte [3] and restated by O'Day.[4]

From the Division of Psychiatric Research, the Boston State Hospital, Mattapan, Mass.

This study was aided by grants from the Commonwealth of Massachusetts and the Rockefeller Foundation.

1. Myerson, A., and Thau, W.: Human Autonomic Pharmacology: IX. The Effect of Cholinergic and Adrenergic Drugs on the Eye, Arch. Ophth. **18**:78-90 (July) 1937.

2. Robertson, D. Argyll: On an Interesting Series of Eye-Symptoms in a Case of Spinal Disease, with Remarks on the Action of Belladonna on the Iris, Edinburgh M. J. **14**:696-708, 1869; Four Cases of Spinal Myosis, with Remarks on the Action of Light on the Pupil, ibid. **15**:487-493, 1869.

3. Uriarte, A. B.: Mouvements pupillaires: Une nouvelle théorie sur la pathogénie du signe d'Argyll Robertson, Ann. d'ocul. **172**:672-687, 1935.

4. O'Day, K.: The Reaction of the Dilator Muscle of the Pupil to Light and Its Bearing on the Argyll Robertson Sign, M. J. Australia **1**:648-650 (May 9) 1936.

Argyll Robertson pointed out that the pathologic lesion is probably in the dilator fibers and that the miosis represents the position assumed by the pupil through paralysis of the dilator muscles. The fact that the pupil reacts to atropine only to a medium degree played an important part in his discussion. He concluded that atropine acts mainly by paralysis of the circular fibers, and perhaps by secondary stimulation of the dilator fibers. When he took all the facts into account, he found it impossible to square them with the theories of pupillary action and, while favoring the hypothesis of injury of the sympathetic fibers, finished the discussion with a statement which concludes his second paper: "For a thorough solution of this question, further experiments and clinical observation are necessary."

This theory of Argyll Robertson's has been overlooked, except by O'Day, and the majority of workers since his time and up to recently have been unaware of certain contradictions between the facts and the theories relating to the Argyll Robertson pupil, especially if the attempt is made to link it with lesions which lie between the afferent fibers from the retina and those connecting with the nucleus of the third nerve. Other workers have added to knowledge of the phenomena which constitute the Argyll Robertson pupil. Thus, the lack of reflex dilatation which takes place either through psychic influences or through pinching the skin of the neck has been adduced as a constant phenomenon of the Argyll Robertson pupil (Merritt and Moore).[5] Babinski's[6] criteria for the Argyll Robertson pupil were: (1) its permanence; (2) the invariability of pupillary immobility whatever the intensity of light or duration of darkness; (3) the dissociation of reflexes, that is, the preservation of the accommodation convergence response and the abolition of the direct and consensual light reflexes, and (4) the frequent bilateral, but occasional unilateral, occurrence of the difficulty. Babinski stated that the pupil is often present in miosis but that it may be normal in size; thus he differed from the original description by Argyll Robertson and diverged from the opinion of certain later authors, especially Merritt and Moore. Finally, a necessary condition is that the retina and oculomotor nerve be normal.

METHODS AND MATERIAL

It is necessary to give a preliminary account of the pharmacologic reactions of the normal eye as our researches demonstrate them to be. We used four drugs as the means of approach: mecholyl (acetylbetamethylcholine hydrochloride); pros-

5. Merritt, H. H., and Moore, M.: The Argyll Robertson Pupil: An Anatomic-Physiologic Explanation of the Phenomenon, with a Survey of Its Occurrence in Neurosyphilis, Arch. Neurol. & Psychiat. **30**:357-373 (Aug.) 1933.

6. Babinski, J.: De l'influence de l'obscuration sur le réflexe des pupilles à la lumière et de la pseudo-abolition de ce réflexe, Rev. neurol. **13**:1214-1218, 1905.

tigmin (dimethylcarbamic ester of m-hydroxyphenyltrimethylammonium methylsulfate); atropine (mandelic ester of tropine), and benzedrine sulfate (racemic benzylmethyl carbinamine sulfate).

Mecholyl is, in the main, a cholinergic drug acting directly on the reacting cells of the eye and producing the following effects on instillation in solutions ranging from 1 to 10 per cent: It narrows the palpebral fissure and constricts the pupil, the light reflex being preserved until the pupil is in complete miosis. The accommodation convergence reflex is likewise preserved. Intra-ocular tension is lessened. Accommodation of the lens for the near point is increased.

Prostigmin, which has its main action on the esterases which inhibit acetylcholine, narrows the palpebral fissure, constricts the pupil in the same way as does mecholyl, decreases intra-ocular tension and increases accommodation of the lens to the near point. The light reflexes are preserved up to the point of complete miosis.

Atropine may be dismissed briefly. It does not widen the fissure. It produces cycloplegia of complete type, so that all reflexes of the pupil, including convergence, and the consensual light response are absent. Accommodation of the lens to the near point is abolished, and intra-ocular tension is increased.

Benzedrine sulfate in solutions ranging from 0.25 to 10 per cent widens the palpebral fissure, dilates the pupil, increases intra-ocular tension, quickly disturbs the accommodation of the lens, so that in full strength there is paralysis of accommodation to the near point, and constricts the vessels of the retina. It is necessary to give in some detail its action on the pupil, since this bears a relationship to its effects on the Argyll Robertson pupil: The pupil dilates with the use of dilute solutions, and the reaction to light is impaired but not destroyed. Thus, while under the effect of a 0.125 or 0.25 per cent solution, the pupil reacts to flash-light. When stronger solutions are used, from 5 to 10 per cent, the pupillary reflex disappears to flash-light but is at all times preserved to bright daylight. In other words, there is a mechanism present which, under the stimulation of bright daylight, overcomes the effect of a strong solution of benzedrine sulfate and brings about the light response.

Patients with indisputable Argyll Robertson pupils were selected. First, the findings in the spinal fluid and blood conformed in every way to those in parenchymatous neurosyphilis. The pupils were completely miotic, pinpoint or not larger than from 1 to 1.5 mm. They did not react to flash-light, to daylight or, just as important in our opinion, to darkness. The convergence reflex was always present and prompt. There was no disease of the nerve head or the oculomotor nerve. The pupils of these patients showed no response to stimulation of the neck, but we think that this is not important, since the reflex is variable and difficult to elicit in normal human beings.

RESULTS

Effect of Atropine, Mecholyl and Prostigmin on the Argyll Robertson Pupil.—We found that the reaction of the Argyll Robertson pupil to atropine was somewhat slower than the normal, and in some instances exceedingly difficult to obtain. However, it was not, as Argyll Robertson believed, of short duration. In fact, we found that in one patient it lasted for two weeks and in the others as long as in the normal subjects.

The main results of this experimentation concern the effects of benzedrine sulfate instilled into the eye. Other drugs, such as mecholyl, prostigmin and atropine, had the reaction that would be expected in normal persons. When the pupil was pinpoint, mecholyl and, similarly, prostigmin had no effect on constriction. If the pupil was somewhat larger, the pupil narrowed when these drugs were instilled into the eye. In other respects, they produced the results expected. The palpebral fissure narrowed on instillation of mecholyl and prostigmin, it did not change with atropine, and widened quite markedly with benzedrine sulfate. The intra-ocular pressure was altered, according to the findings given previously. The accommodation of the lens corresponded closely to the normal. It is the effect of benzedrine sulfate on the pupil which is remarkable and, we believe, unique in the literature concerning the Argyll Robertson pupil.

Effect of Instillation of Benzedrine Sulfate into the Eyes of Patients with the Argyll Robertson Pupil.—The fissure widened, we believe, to the full extent found in normal persons. With dilute doses dilation of the pupil took place almost, if not quite, as well as in the normal pupil. Concentrations of 0.25 per cent, or even less, given in the quantity of two or three drops, produced fair dilatation of the pupil, that is, not to the point of complete mydriasis but up to 5 or 6 mm. This ordinarily took place within thirty minutes.

The reaction of the dilated pupil to light was as follows: First, it reacted to darkness by slow dilatation. If the pupil was observed in a dark room by the light of a small match, which had no effect on any pupil, it was seen that the size of the pupil had increased from that observed in the light, in several instances 2, 3 and 4 mm. When the patient was removed from the dark room to one which was well lighted by the sun, without standing directly in the sunlight, the following reactions were observed: (1) The palpebral fissure narrowed, as takes place in all normal persons. This reaction of the palpebral fissure seems to us to be part of the light reflex. (2) The pupil rather slowly, but definitely and unmistakably, narrowed, not to the point of the original miosis or to that to which normal pupils contract but to one somewhere between the original size and that produced by darkness.

In some instances there was present in the darkness a reflex to flash-light; in others, if the pupil was continually played on by the flash-light it grew definitely smaller, but in a deliberate way. In some cases restoration of the consensual light reflex occurred, to very limited degree, to be sure, but definitely, so that all observers noted it. These phenomena lasted several hours; the pupil gradually came back to its

original miotic position and on the following day had again the characteristics of the Argyll Robertson pupil.

Repeated for several days intramuscular injections of 30 to 40 mg. of benzedrine sulfate produced in most subjects: (1) some widening of the pupil, which increased in diameter from 1 to 2 mm. and showed a moderate reaction to darkness, and (2) a very moderate reaction to bright light, although not to flash-light. We could not observe that a consensual light reflex took place in all cases, although it occurred in some instances.

DEFINITION OF THE INCOMPLETE ARGYLL ROBERTSON PUPIL

We may state that the nonmiotic pupil which does not respond to flash-light and reacts in accommodation is not a complete Argyll Robertson pupil. If a person whose pupils are 2, 3 or 4 mm. wide and seem fixed to light is taken into a dark room, it will be noted that the pupils, if examined by the light of a match, are wider than they were in ordinary room light. Furthermore, if the same person is removed to a brightly lighted room into which the daylight streams, even though he is kept out of the direct sunlight, it will be found that the pupils react slowly but definitely to the stimulation of daylight. A typical case is cited.

In the case of A. S., a man with typical tabetic dementia paralytica, the width of the pupils in a moderately lighted room was: right, 6.5, and left, 5 mm. Stimulation with a bright flash-light did not move the pupils. The accommodation reflex was adequate. In complete darkness the pupils reached 7 and 5.5 mm., respectively, which was not a marked change, since they were fairly well dilated to begin with. However, in a well lighted room in the laboratory the pupils altered definitely in size, the right becoming 4 and the left 3 mm. in diameter. We can state positively that even with pupils 2, 2.5 and 3 mm. in width, the same dilatation in darkness and reaction to direct sunlight obtain. This does not occur with the pinpoint pupil or with those which are 1 mm. or less in width to begin with.

It is necessary, therefore, to state that no pupil is adequately studied for the Argyll Robertson phenomenon until at least the following tests have been made: (1) tests for the reactions of the pupil to flash-light and in accommodation in the usual fashion and (2) observations on the width of the pupil in darkness and (3) observations on the width of the pupil in a room illuminated by daylight.

The complete Argyll Robertson pupil is one which is miotic at the pinpoint stage or thereabouts and which does not react to flash-light, darkness or daylight but reacts in accommodation. Such other phenomena as widening of the pupil on stimulation of the neck are too uncertain and, while relevant to theory, are not fundamentally essential in practice. It must, of course, be assumed that there is no disease of the retina and no mechanical limitation of the motions of the iris.

It is apparent, therefore, that the controversy in the literature [7] in which miosis is held up as the sine qua non of the Argyll Robertson pupil may be settled by stating that both parties are in part correct and in part incorrect. The somewhat dilated pupil which does not react to flash-light but reacts in accommodation is merely an incomplete Argyll Robertson pupil and will, as already stated, respond to darkness and to bright daylight. The completely miotic pupil is the complete Argyll Robertson pupil, and the difference between the two pupils is merely that in the one case the dilator fibers still have power and in the other all power in these fibers has disappeared.

COMMENT

We do not intend to discuss the general literature on the subject. This has been ably done by a series of writers and, in recent times, by Schmelzer,[8] Lagrange and Lagrange,[9] McAndrews,[10] Merritt and Moore [5] and others.[11]

7. Abramson, J. L., and Teitelbaum, M. H.: The Argyll Robertson Phenomenon in Multiple Sclerosis, Am. J. Ophth. **16**:676-682, 1933. Dejerine, J.: Sémiologie des affections du système nerveux, Paris, Masson & Cie, 1914. Magoun, H. W., and Ranson, S. W.: The Central Path of the Light Reflex: A Study of the Effect of Lesions, Arch. Ophth. **13**:791-811 (May) 1935. Scala, N. P., and Spiegel, E. A.: The Pupillary Reactions in Combined Lesions of the Posterior Commissure and of the Pupillodilator Tracts, ibid. **15**:195-216 (Feb.) 1936. Wilson, S. A. K.: Modern Problems in Neurology: The Argyll Robertson Pupil, London, Edward Arnold & Co., 1928, p. 33.

8. Schmelzer, H.: Berichte ueber die ophthalmologische Literatur, Ztschr. f. Augenh. **81**:70-88, 1933.

9. Lagrange, H., and Lagrange, A. M. H.: L'abolition isolée du réflexe pupillaire d'adaptation à la lumière (La valeur sémiologique du signe d'Argyll Robertson), Ann. d'ocul. **172**:631-672, 1935.

10. McAndrews, L. F.: Argyll Robertson Pupil, Arch. Ophth. **10**:520-534 (Oct.) 1933.

11. Budge, J.: Ueber die Bewegung der Iris, Braunschweig, Friedrich Vieweg u. Sohn, 1855. Dupuy-Dutemps, L., and Cestan, R.: Le signe pupillaire d'Argyll-Robertson: Sa valeur séméiologique; ses rélations avec la syphilis, Gaz. d. hôp. **74**:1433-1442, 1901. Haguenau, J., and Ledoux-Lebard, G.: Le signe d'Argyll-Robertson est-il toujours d'origine syphilitique? Deux cas d'abolition du réflexe photomoteur avec conservation du réflexe accommodation-convergence sans signe d'Argyll-Robertson, Rev. neurol. **1**:570-580 (April) 1934. Illing, E.: Ueber Pupillotonie (tonische Konvergenzreaktion scheinbar lichtstarrer Pupillen), Monatschr. f. Psychiat. u. Neurol. **85**:135-144, 1933. Poos, F., and Grosse-Schönepauck, H.: Studien an der lichtstarren Pupille: I. Die lichtstarre Pupille als pharmakologisches Testobjekt, Arch. f. Ophth. **135**:144-158, 1936. Ranson, S. W., and Magoun, H. W.: The Central Path of the Pupilloconstrictor Reflex in Response to Light, Arch. Neurol. & Psychiat. **30**:1193-1204 (Dec.) 1933. Spiegel, E. A.: Die Zentren des autonomen Nervensystems (Anatomie, Physiologie und topische Diagnostik), Berlin, Julius Springer, 1928. Winawer, B.: Le signe d'Argyll-Robertson: Étude anatomique, physiologique, pathogénique et séméiologique, Thèse de Paris, no. 154, 1912.

Since his was the first radical theory for the explanation of the Argyll Robertson pupil, Uriarte [3] started with the hypothesis that the reaction of the pupil to light is brought about through operation of the law of reciprocal relationship and that the constrictor reaction of the pupil must be regarded, first, as paralysis of the dilator muscle and, second, as excitation of the constricting muscle of the iris, while dilatation of the pupil to darkness or diminished light is an active process brought about through the sympathetic fibers with the concomitant relaxation of the constrictor fibers, the nervous source of the chain of events being the retina.

Thus, the Argyll Robertson pupil, according to Uriarte, is one in which the dilator fibers have been paralyzed or impaired so that no dilatation to darkness takes place. Consequently, the pupil finally assumes a constricted position, in which attitude or posture it remains largely or entirely because there are no fibers capable of changing it by activity of the dilator mechanism.

Rochon-Duvigneaud,[12] in a study of the motility of the pupil in the inferior vertebrates—tortoises, lizards and diurnal serpents—found that they have no pupillary movements, or that these responses were merely indicated, while nocturnal animals in the same zoological scale have true pupillary light responses. This author stated that pupillary movements are adaptations to nocturnal vision and act also as a defense against intense luminosity.

Concerning this matter, O'Day [4] may be quoted as follows:

> There is some embryological evidence that the dilator is actively concerned with the light reflex. Like the sphincter, it is developed from ectoderm—the outer layer of the optic vesicle. But while the sphincter develops fully into unstriated muscle, the dilator remains in a semi-embryonic state, only the anterior part of the cell being transformed into muscle fiber, and it becomes "not a true muscle, but a contractile membrane of epithelial origin." It thus bears a remarkable resemblance to the pigment epithelium of the retina of which layer, in actual fact, it is the forward continuation. Although it has never been proved in man, it is known that in lower animals the cells of the pigment epithelium of the retina send processes inwards between the outer members of the rods and cones. Under the influence of light the processes elongate inwards, and in the dark contract outwards. The muscle fibers of the dilator are nothing more than the processes of the cells of the anterior of the two posterior layers of epithelium of the iris, and their action is exactly the same as that of the processes of the retinal pigment epithelium. In the light they elongate, and in the dark they contract. The comparison may seem fanciful. It is nevertheless striking. The semi-embryonic state of development of the dilator would also explain why the pupil will contract to light after all the central connexions have been destroyed. Although this primitive reaction is commonly attributed to the sphincter, it seems more probable that it might be retained by the more primitive dilator, the cells retaining their property of responding directly to a light stimulus.

12. Rochon-Duvigneaud, A.: Structure et forms du cristallin, Ann. d'ocul. **172**:563-587, 1935.

Our own experiments definitely show that there are two sets of important facts which must be reconciled. First, benzedrine sulfate instilled in the normal eye tends directly to injure the light reflex, although the pupil definitely dilates. Strong solutions, from 1 to 10 per cent, produce a pupil which is fairly rigid to flash-light but always retains the power to contract to bright daylight and, in fact in some respects, resembles a dilated incomplete Argyll Robertson pupil. The Argyll Robertson pupil, however, when treated with dilute solution of benzedrine, becomes more mobile to light and regains in part its normal activity. This contradiction can be reconciled by assuming that in the normal eye there exists a balance between sympathetic and parasympathetic impulses. This is disturbed by overstimulation of the fibers of the dilator muscle by benzedrine, which results in overpowering of the constrictor muscle, so that it will not respond to the weak stimulation set going by flash-light but will again become potent when the power of daylight to manufacture acetylcholine is brought into play. It has been shown definitely by Velhagen[13] that daylight brings about the manufacture of acetylcholine in the eye.

We may postulate that in the Argyll Robertson pupil there is lack of adrenergic substances or sympathetic stimulation, and that by supplying this substance by instillation or by injection the pupil dilates, according to the well established fact that a muscle will respond to either adrenergic or cholinergic substances, even when its nerve supply has been impaired or removed. That is, the iris, like other smooth muscles, has the native property of responding to benzedrine, and consequently its dilating capacity is, in part, restored by this chemical. Therefore, the pupil widens in darkness, and with relaxation of the dilator fibers under the influence of daylight, it gradually narrows. The normal balance has not, however, been restored. Consequently, the reaction is slow, but enough direct stimulation of the dilator muscle has been produced by the drug to restore in part the normal responses.

We do not state that it is merely the injury to the dilator muscle or the dilator fibers which is responsible for the Argyll Robertson pupil. With a dilute solution of benzedrine sulfate (from 0.125 to 0.25 per cent), the normal pupil dilates and the quick, sharp reaction to light is maintained. Comparing this reaction with that of the Argyll Robertson pupil under similar circumstances is like comparing the hare and the tortoise. The normal pupil responds sharply, even though it may be no more dilated than the Argyll Robertson pupil, while the latter responds deliberately. Therefore, it seems to us that there must be postulated also some injury to the constrictor mechanism. We believe

13. Velhagen, K.: Zur Frage der vagotropen Substanzen im Auge, Arch. f. Augenh. **105**:573-602, 1932.

that Uriarte has gone too far in his hypothesis. It is as necessary biologically for the pupil to guard the eye against excessive stimulation as for it to widen in darkness. It is not necessary to throw the baby out with the bath to establish the importance of the dilator mechanism in the reaction of the pupil to light and in the genesis of the Argyll Robertson pupil.

We do not offer here any theory of genesis of the Argyll Robertson pupil. We point out that it is possible that there is a local injury to the iris muscle or to the tissue of the iris itself. It is conceivable that if the substance of the iris becomes more rigid, the muscles which pull it to and fro may become incompetent, even though they are in a fairly normal state. Moreover, the muscles themselves may be directly involved, with the dilator muscle more affected than the constrictor. So far as we know, no direct, that is, no anatomicohistologic, studies have been made on the iris in cases of neurosyphilis. These are needed before the local mechanisms of the eye are excluded as factors in the production of the Argyll Robertson pupil.

SUMMARY

1. The complete Argyll Robertson pupil is one in which the pupil is miotic to the extreme point and there is no reaction to darkness, flash-light or daylight, while the reaction in accommodation is preserved. In our opinion, other reflexes are not clinically essential.

2. The incomplete Argyll Robertson pupil is one in which there is some dilatation of the pupil. This pupil does not react to flash-light but will widen slowly in the darkness and constrict slowly in a room well illuminated by daylight.

3. The light reflex may be restored in a partial way in the Argyll Robertson pupil by instillation of a dilute solution of benzedrine sulfate, ranging from 0.125 to 0.5 per cent, or by repeated subcutaneous injection or oral ingestion of the drug. Under such circumstances the pupil dilates, and while ordinarily only slightly mobile to flash-light, it widens in darkness and constricts in daylight, the movements of dilatation and constriction being slow and deliberate but certain.

4. The light reflex, so far as the pupil is concerned, must be considered as made up of two important parts: (1) dilatation of the pupil to darkness or to partial illumination and (2) constriction to light, these movements being brought about by the reciprocal activities of the sympathetic and the parasympathetic nervous system, or, to speak chemically, by a balance between adrenergic and cholinergic substances. Furthermore, part of the light reflex is widening and narrowing of the palpebral fissure, widening taking place in darkness or in lessened illumination and constriction under the influence of light or increased illumination.

AUTONOMIC AND MOTOR LOCALIZATION IN THE HYPOTHALAMUS

LÉON ECTORS, M.D.*

NORRIS L. BROOKENS, PH.D.

AND

R. W. GERARD, M.D.

CHICAGO

Present knowledge of the function of the hypothalamic regions has been obtained in various ways. Destruction of localized areas within the hypothalamus has demonstrated centers for: water balance (Bailey and Bremer;[1] Camus and Roussy;[2] Fisher, Ingram and Ranson[3]); carbohydrate metabolism (Davis, Cleveland and Ingram;[4] Roussy and Mosinger[5]); the rhythm of sleep (Hess;[6] Ranson and Ingram[7]), and regulation of body temperature (Ranson and Ingram;[8] Isenschmidt and Schnitzler[9]). The presence of a sleep center here was first indicated by the anatomic and pathologic studies of von Economo[10] (1930). Bard[11] compared the behavior of hypothalamic cats, with the cortex and thalamus removed, and that of decerebrate cats in which the hypothalamus in addition had been removed and showed that the hypothalamus is a center for manifestation of the emotions, particularly rage.

From the Department of Physiology, the University of Chicago.

* Belgian Fellow of the C. R. B. Educational Foundation, Inc.

1. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

2. Camus, J., and Roussy, G.: J. de physiol. et de path. gén. **20**:509, 1922.

3. Fisher, C.; Ingram, W. R., and Ranson, S. W.: Relation of Hypothalamico-Hypophyseal System to Diabetes Insipidus, Arch. Neurol. & Psychiat. **34**:124 (July) 1935.

4. Davis, L.; Cleveland, D., and Ingram, W. R.: Carbohydrate Metabolism: Effect of Hypothalamic Lesions and Stimulation of Autonomic Nervous System, Arch. Neurol. & Psychiat. **33**:592 (March) 1935.

5. Roussy, G., and Mosinger, M.: Ann. de méd. **33**:193, 1933.

6. Hess, W. R.: Compt. rend. Soc. de biol. **107**:1333, 1931.

7. Ranson, S. W., and Ingram, W. R.: Am. J. Physiol. **101**:690, 1932.

8. Ranson, S. W., and Ingram, W. R.: Proc. Soc. Exper. Biol. & Med. **32**: 1439, 1935.

9. Isenschmidt, R., and Schnitzler, W.: Arch. f. exper. Path. u. Pharmakol. **76**:202, 1914.

10. von Economo, C.: J. Nerv. & Ment. Dis. **71**:249, 1930.

11. Bard, Philip: Am. J. Physiol. **84**:490, 1928.

Stimulation (Karplus and Kreidl [12]) demonstrated an orthosympathetic center in the hypothalamus, for from it are obtained such typical sympathetic reactions as pupillary dilatation, increase in the blood pressure and respiration and pilomotor contraction; the presence of parasympathetic centers is indicated as well, for Beattie and his co-workers [13] found increased motor activity of the stomach and intestines and cardiac arrhythmia with no modification in respiratory rate and, more recently,[14] an increase (and also a decrease) in bladder tone. Separate representation in the hypothalamus of the two parts of the autonomic system (Cushing [15]) is only roughly established; indeed, sleep has been produced by stimulation (Hess [6]) and by destruction (Ranson and Ingram [7]) of supposedly the same hypothalamic region. Perhaps the discordance of results is due to the difficulty in reaching this region of the brain.

Karplus and Kreidl [12] stimulated the rough surface of the hypothalamus, exposed by various transverse sections, while Ranson and his co-workers [16] used the Horsley-Clarke apparatus. With this instrument, extensive exploration was made of points influencing blood pressure, respiration and bladder tone. Both groups of investigators concluded that the hypothalamus is only an orthosympathetic center, but emphasized the possibility of the passage of parasympathetic tracts through the area. Beattie and his co-workers [13a] stimulated the wall of the third ventricle but, unfortunately, did not describe their method, nor can one accurately interpret the drawings. Their experiments indicated a parasympathetic center in the hypothalamus.

The motor part of the frontal lobe has been shown also to be sympathicomotor. Stimulation of certain areas here results in increased blood pressure (Hoff and Green [17]), and extirpation of the frontal lobe leads to disturbances in vasomotor control and in gastro-intestinal movements (Fulton, Kennard and Watts [18]). There is also evidence of a sympathicosensory function in this region (Dusser de Barenne [19]).

12. Karplus, J. P., and Kreidl, A.: Arch. f. d. ges. Physiol. **215**:667, 1927.

13. (a) Beattie, J.; Brow, G. P., and Long, C. H.: A. Research Nerv. & Ment. Dis., Proc. **9**:249, 1930. (*b*) Beattie, J.: Canad. M. A. J. **26**:278, 1932.

14. Beattie, J., and Kerr, A. S.: Brain **59**:302, 1936.

15. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic System, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

16. (*a*) Ranson, S. W.; Kabat, H., and Magoun, H. W.: Am. J. Physiol. **109**: 85, 1934; (*b*) Autonomic Responses to Electrical Stimulation of Hypothalamus, Preoptic Region and Septum, Arch. Neurol. & Psychiat. **33**:467 (March) 1935. (*c*) Kabat, H.; Magoun, H. W., and Ranson, S. W.: J. Comp. Neurol. **63**:211, 1936.

17. Hoff, E. C., and Green, H.: Am. J. Physiol. **117**:411, 1936.

18. Fulton, J. F.; Kennard, M. A., and Watts, J. W.: Am. J. Physiol. **109**:37, 1934.

19. Dusser de Barenne, J. G.: Quart. J. Exper. Physiol. **9**:355, 1915; Proc. Roy. Soc., London, s.B **96**:272, 1924.

In view of the conflicting results, a technic permitting direct stimulation of the uninjured hypothalamus under visual control is desirable, though the same certainty of localization can be obtained, more laboriously, with an adequate series of animals by the Horsley-Clarke apparatus and histologic control. The method presented here is simple and satisfactory.

METHOD

With the animal under light ether or pentobarbital sodium anesthesia the trachea is cannulated and the cat placed on a board with a special jaw clamp. The skin and the temporal muscle are reflected to expose completely one side of the skull, which is then removed by trephine and rongeur to lay bare the entire hemisphere, the longitudinal sinus being saved. The dura is then incised crucially and reflected over the cut edges of the bone, thus controlling bleeding. A thin, blunt strip (e. g., a forceps handle) is introduced into the longitudinal fissure and the exposed hemisphere pushed laterally to reveal the corpus callosum; the field is dried with long, thin, trimmed cotton pledgets wrung out after being soaked in Ringer's solution.

The entire left half of the brain is then removed with two strokes of a dull scalpel. The knife is inserted vertically in the midline until the point reaches the base of the skull. To avoid injury of the third ventricle, the head is previously rotated by means of the clamp, so that the point of the knife strikes about 5 mm. lateral to the midline. The blade is first swept forward, cutting all structures, and then backward and somewhat laterally, so that the brain stem is intact well above the colliculi. The result is incomplete hemidecerebration. At the end of the stroke, the brain is scooped out with the knife and the resulting cavity immediately plugged with cotton soaked in warm Ringer's solution. Considerable pressure is exerted on the cotton to compress against the bone the vessels at the base of the brain and thus stop bleeding. The animal shows little shock after this procedure.

When bleeding is stopped, ordinarily in a few minutes and with loss of only a few cubic centimeters of blood, the third ventricle is opened by wiping away the remaining sheet of tissue with cotton rolled into cigar-shaped pledgets, about 15 mm. long and 2 or 3 mm. thick, wrung out after soaking in Ringer's solution. These are held in a forceps and used as probes. With the choroid plexus as a landmark, the ventricle is best entered in the posterior region, and appears as a thin slit. The gray commissure or massa intermedia of the thalamus is then cut through with fine scissors; the remaining wall is wiped away, and the exposure is complete, down to the fine opening of the stalk of the hypophysis. Observations may begin almost immediately, for there is little shock. To permit free movement, the animal is suspended from a horizontal bar by means of towel clips hooked under the supraspinous ligaments near the pelvic and shoulder girdles, and into the skin and superficial muscles of the head.

Induced shocks from a Harvard inductorium were used, with 6 volts in the primary. Generally, definite responses were obtained with the secondary at from 10 to 12 cm., when the shocks could just be felt on the tongue. Tests were always begun with subminimal shocks, which were then increased until a definite response was obtained. A concentric electrode, made by pushing an enameled copper wire through an 18 gage hypodermic needle, with the final half inch bent at 75 degrees and the end cut off square, permitted well localized stimulation (referred to later). A barely visible extravasation marked the point of stimulation, so that accurate repetition was insured.

It must be emphasized that these stimuli were not excessive. As tested on an oscillograph, our long, closely approximated leads delivered only two thirds of the

voltage obtainable at the secondary terminals. Further, the shock strength with 6 volts in the primary and with the secondary at 12 cm. and tilted at 65 degrees is the same as that with 1.5 volts in the primary and the secondary at 12 cm. and in a horizontal position. Finally, the concentric character of the electrodes tends to concentrate the flow of current and minimize spread beyond the outer tube.

Respiration was measured with a tambour connected to a side arm of the tracheal cannula, and blood pressure, with a mercury manometer connected to the femoral artery. Bladder tone was obtained with a water manometer connected to a cannula inserted through the urethra and protruding into the lumen of the bladder, and stomach tone, with a manometer connected to a balloon in the stomach.

RESULTS

Two, or really three, areas on the wall of the third ventricle yielded sympathetic and motor responses on stimulation. A completely silent

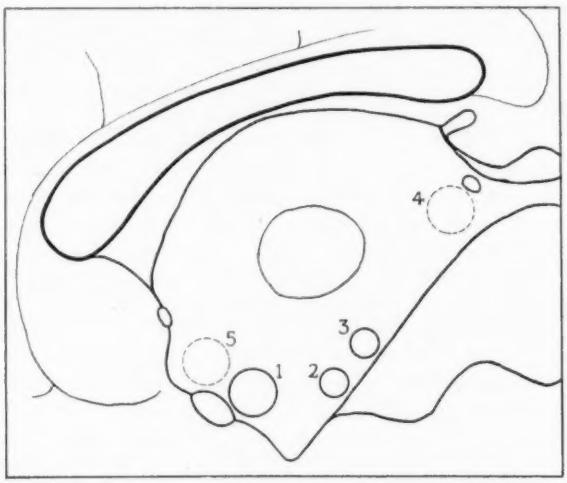

Fig. 1.—*1* indicates the anterior area; *2*, the rostral portion of the posterior area; *3*, the caudal portion of the posterior area; *4*, the area giving on stimulation the sum of responses from areas *1*, *2* and *3*, and *5*, the area giving no response on stimulation alone, but causing inhibition of after-discharge following stimulation of areas *2* and *3*.

region separated them. The anterior responsive region corresponded to the supra-optic and anterior hypothalamic nuclei, and the posterior pair, to the posterior hypothalamic nucleus. The intervening nonresponsive area corresponded to the infundibular nucleus, the hypothalamic periventricular nucleus and the dorsal median and ventral median hypothalamic nuclei (fig. 1). The nomenclature follows that of Ingram, Hannett and Ranson.[20]

The anterior area (point *1*, fig. 1), above the posterior border of the optic chiasm, is approximately 5 mm. in diameter, maximal responses

20. Ingram, W. R.; Hannet, F. I., and Ranson, S. W.: J. Comp. Neurol. **55**: 333, 1932.

being elicited in all animals from the same central point and decreasing slightly to the periphery. A stimulus of threshold strength at the center was effective also at the periphery; so this gradation is not due to spread of the current. Also, the margin of the excitable area was sharp; moving the electrode less than 1 mm. abolished all response. The responses were a complex of motor and orthosympathetic activities and did not begin until a latent period of from two to four seconds had elapsed after the start of stimulation. Then there occurred: bilateral opening of the palpebral fissures, retraction of the upper and lower eyelids, protrusion of the eyeballs and marked dilatation of the pupils, respiratory and circulatory changes, contraction of the bladder and somatic movements.

The respiratory rate accelerated moderately—from 35 to 50 per minute—but the amplitude increased at least three times, so that the main effect was an increase in depth (fig. 2*A*). The blood pressure rose sharply—on the average, 30 mm. of mercury. The high level was maintained about two seconds and then began to drop gradually, even if stimulation was continued. When stimulation ceased, there was a further slight drop, followed immediately by a marked rebound, with increases of from 25 to 30 mm. before the pressure finally fell to normal (fig. 2*C*). Identical changes were found in curarized animals. No alteration of stomach tone was noted, but in about half the animals the urinary bladder contracted after a latency of from five to ten seconds.

No somatic movements of the limbs or back occurred, but the muscles of the neck showed a slight increase in tone, which resulted in some lifting of the head. Contraction of the facial and masticatory musculature gave an expression closely simulating rage or anger.

The posterior or supramamillary area, corresponding to the posterior hypothalamic nucleus, may be divided into a caudal and a rostral portion, each about 3 mm. in diameter. The responses obtained on stimulation of the caudal portion were mainly tonic, and those from the rostral portion, clonic.

Stimulation of the caudal portion (point *3*, fig. 1) led to: bilateral retraction of the eyelids, pupillary dilatation and protrusion of the eyes; unilateral pilomotor erection on the ipsilateral side; tonic contraction of the respiratory muscles with stopping of respiration in inspiration, and a marked increase in blood pressure (averaging 30 mm. of mercury), which fell off before the end of stimulation. The blood pressure continued to fall after stimulation had ceased, and the heart rate often became slower as well. This is in sharp contrast with the vasomotor consequences of stimulating the anterior hypothalamic nucleus, which always left the circulatory system in seemingly better tone, with higher blood pressure and faster heart rate. Gastric motility was not changed, but in about half the experiments contractions of the bladder took place after from five to ten seconds.

The head and body were bent so as to produce a concavity directed toward the ipsilateral (stimulated) side; the ipsilateral limbs were flexed at all joints and the contralateral ones extended, and the tail was lifted. A facial expression appeared that can best be described as that of sham pain. The whole posture was strongly tonic and was held through the duration of the stimulus. When stimulation ceased, rhythmic running movements with all four limbs, lashing of the tail and panting began

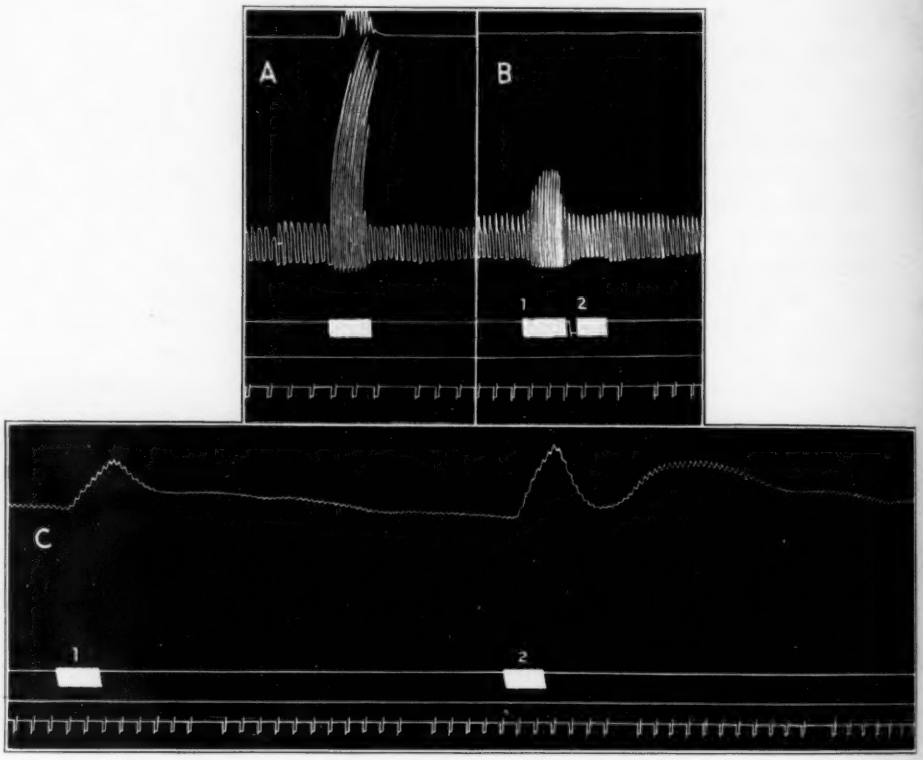

Fig. 2.—*A* shows increase in the depth of respiration on stimulation of the anterior hypothalamic nucleus (point *1* of figure 1); *B*, increase in the speed of respiration on stimulation of the posterior hypothalamic nucleus of the same animal (*1* indicating stimulation of point *2* of figure 1, and *2*, stimulation of the supraoptic region), and *C*, increases in blood pressure, with the mercury manometer connected to the right femoral artery. *1* indicates stimulation of the posterior hypothalamic nucleus (point *2* of figure 1), and *2*, stimulation of the anterior hypothalamic nucleus (point *1* of figure 1).

promptly and lasted up to five minutes. This after-effect is exactly similar to the somatic movements occurring during stimulation of the rostral portion of the posterior region.

Stimulation of the rostral portion of the posterior area (point *2*, fig. 1) led to the same optic, pilomotor and bladder responses as did stimulation of the caudal portion. The blood pressure was also increased, to like extent with and without curare. Respiration was markedly accelerated, from an average rate of 35 to one of 65 per minute, but the amplitude of movements was only slightly increased (fig. *2B*). The nares, face and tongue made small movements synchronous with respiration, giving an appearance of panting. This marked increase in rate is in contrast with the response on stimulating the anterior nucleus, which was mainly an increase in amplitude.

The head was rotated on the longitudinal axis, with the snout directed to the stimulated side; the back was bent, with the concavity directed toward the same side; the limbs showed walking or running movements accompanied by lashing of the tail, and a facial expression of sham fear appeared. These phenomena did not cease or alter after stimulation ended but continued for some time, in one case seven minutes.

The running movements, both during and after stimulation, could be changed by peripheral stimulation. Pinching any part of the body stopped the limbs in extension. Light touch on the plantar surface of the foreleg, however, caused the leg to stop at once in any position and led to marked flexion of the toes which resembled a grasping movement; similar stimulation of the dorsal surface of the moving limb changed the pattern of the movement so that the leg stepped accurately over the obstruction. If the lashing tail came into contact with a foreign object, it ceased to wave but curled around the object and tended to grasp it.

Stimulation of the preoptic and supra-optic regions (point *5*, fig. 1) alone had no effect, but promptly and completely inhibited the after-effect of stimulation of the posterior hypothalamic regions. The panting and running movements stopped, and the facial expression of fear disappeared. Stimulation of the thalamic surface of the third ventricle gave no response; stimulation of the pretectal region led to constriction of the pupils and closing of the eyelids, and that of the anterolateral wall of the aqueduct of Sylvius (point *4*, fig. 1), to strong running movements with increase in the blood pressure and panting.

All the responses described were obtained alike with the animal under light ether and under pentobarbital sodium anesthesia. Increasing depth of anesthesia diminished all the responses and finally abolished them in regular order. The somatic changes disappeared first, then those of respiration and finally the vasomotor and pupillary responses. The latent period, from two to four seconds, was as long for the somatic as for the sympathetic responses.

In all cases, pushing the electrode into the ventricular wall a millimeter or two abolished the response obtained from the surface. This,

plus the sharp lateral limits of excitable regions, is evidence of the limited spread of current in these experiments and of the localization of excitable masses. No noticeable injury was produced by stimulation, since, even after very strong shocks, the same responses could be obtained repeatedly hour after hour.

COMMENT

Our findings show clearly the existence of diencephalic centers of autonomic and somatic motor character. Further, there is definite localization of function as between the anterior and the posterior region of the lower part of the wall of the third ventricle. The somatic and the autonomic responses are obviously related. Both appear together after the same latency and are of a character appropriate to each other. Thus, from the anterior region the facial expression of rage is evoked with its autonomic and respiratory concomitants, while from the posterior region are obtained the manifestations of fear or pain. Such integrated behavior strongly indicates that these observations are physiologically valid, due to stimulation of functional units, rather than a potpourri of effects resulting from the excitation of independent structures accidentally associated in the path of a spreading current.

The respiratory changes—predominant increase in amplitude from the anterior portion of the hypothalamus and in rate from the posterior portion—are in harmony with the results of Crouch and Elliot,[21] who stimulated the same regions with the aid of the Horsley-Clarke apparatus. Otenasch and Lilienthal [22] showed, by successive transections, that panting movements persisted when the anterior portion of the hypothalamus was removed but the posterior portion remained—further evidence of the existence of separate centers controlling rate and amplitude. Bogen [23] offered evidence that there are chemically distinct controls for the rate and the depth of respiration.

Despite some negative findings (Leiter and Grinker [24]), there is now general agreement on the existence of vasomotor centers in the hypothalamus (Karplus and Kreidl;[12] Beattie;[13b] Ranson, Kabat and Magoun,[16b] and Crouch and Elliot [21]). Separation of the effects of stimulation of the anterior and those of the posterior region, such as are presented here, has not previously been demonstrated clearly. Pupillary changes following hypothalamic stimulation have been studied most

21. Crouch, R. L., and Elliot, W. H., Jr.: Am. J. Physiol. **115**:245, 1936.

22. Otenasch, F. J., and Lilienthal, J. L.: Am. J. Physiol. **116**:117, 1936.

23. Bogen, E.: Am. J. Physiol. **85**:352, 1928.

24. Leiter, L., and Grinker, R. R.: Role of Hypothalamus in Regulation of Blood Pressure: Experimental Studies, with Observations on Respiration, Arch. Neurol. & Psychiat. **31**:54 (Jan.) 1934.

recently by Ranson and Magoun,[25] and contraction of the urinary bladder, by Ranson, Kabat and Magoun [16b] and Kabat, Magoun and Ranson.[16c] Our observations are in harmony with theirs.

Karplus and Kreidl [12] and Ranson and his co-workers [16b] on stimulating the hypothalamus obtained sympathetic responses throuhout its length and inclined to the view that the most anterior responding region was the sympathetic center and that its efferent tract was engaged more caudally. The present findings suggest rather the existence of several discrete centers in the hypothalamus, distributed anteroposteriorly, the tracts of which become associated only more posteriorly. At least, on stimulation of the wall of the aqueduct as it leaves the third ventricle (point *4*, fig. 1) there results a mixture of the various responses obtained discretely from the separate, more anterior regions. Respiration, for example, is markedly increased in both rate and amplitude. Incidentally, the presence of several centers giving qualitatively discriminate responses in which somatic and autonomic effectors cooperate indicates for the hypothalamus a "higher" rôle than that of a center for a general and indiscriminate orthosympathetic discharge in emergencies (Cannon [26]).

Further, Ranson has assigned a lateral position to the hypothalamic sympathetic center. Responses from medial regions, where we find them, he attributed to stimulation of tracts crossing in the supramamillary and supra-optic decussations. In fact, our anterior region is, almost surely, the supra-optic commissure in which Kabat, Magoun and Ranson [27] and Kabat [28] found activity to the midline. Their more posterior reactive region may also correspond to ours, since like effects resulted from stimulation. It is significant, however, that tracts are mainly gathered laterally and centers more medially; so, although we have not explored the lateral portion of the hypothalamus adequately, we incline to the reverse interpretation.

Somatic motor responses from the hypothalamus have been previously observed and variously interpreted. Struggling movements on stimulation occurred in the experiments of Ranson and his co-workers [16b] after a longer latency than that for the sympathetic effects, and were interpreted as due to a separate system not related to the hypothalamus. In our experience, the two were always closely associated.

25. Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179 (June) 1933.

26. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, ed. 2, New York, D. Appleton & Company, 1929.

27. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of Points in Forebrain and Midbrain: Resultant Alterations in Blood Pressure, Arch. Neurol. & Psychiat. **34**:931 (Nov.) 1935; footnote 16c.

28. Kabat, H.: J. Comp. Neurol. **64**:187, 1936.

The acute experiments of Hinsey, Ranson and MacNattin [20] proved that the posterior portion of the hypothalamus must be intact for locomotion, since its destruction leads to disturbed equilibrium and failure of the walking mechanism. Bard,[11] likewise, found that the chronic diencephalic cat could walk, run and express rage in a manner impossible to the decerebrate animal. We also observe walking and running movements on stimulation of the posterior portion of the hypothalamus alone. Besides coordinated movements, with their tonic concomitants, maintained tonic postures are also elicited from the hypothalamus. These are analogous to the tegmental reaction described by Ingram and his co-workers [30] in the mesencephalon and probably represent tonic components of standing. Cutaneous stimulation of the plantar aspect of the foot during this response induces a flexor movement of the toes, and similar stimulation of the tail causes it to curl around the stimulating object. Such findings strongly suggest a localized center for postural locomotion and for grasping. The hypothalamus, like frontal areas 4 and 6 (Fulton, Kennard and Watts [18]), thus seems to be both sympathetic and motor. Whether the frontal lobe has autonomic properties by virtue of connections with the hypothalamus or the hypothalamus manifests motor properties via connections with the cortical or subcortical motor systems or both regions have direct motor and sympathetic connections with the lower neuraxis remains to be determined.

SUMMARY

A method is described of stimulating the lateral wall of the third ventricle of the hemidecerebrate cat under direct visual control. Stimulation reveals several distinct autonomic and somatic motor centers and one inhibitory "center." An anterior hypothalamic (supra-optic) nucleus gives optic, respiratory, circulatory and somatic responses suggestive of rage; the rostral part of a posterior region, those of fear, and its caudal part, those of pain. Stimulation of the anterior region increases the depth of the respiration and, both immediately and for longer periods, the blood pressure. Stimulation of the posterior region increases the respiratory rate and, after a temporary rise, lowers the blood pressure. Somatic effects are obtained almost exclusively from the posterior region—characteristic tonic postures (grasping) during stimulation of its caudal portion, and coordinated running, stepping and other movements during and after stimulation of the rostral portion and after stimulation of the caudal part.

29. Hinsey, J. G.; Ranson, S. W., and McNattin, R. F.: Tr. Am. Neurol. A. **55**:128, 1929.

30. Ingram, W. R.; Ranson, S. W.; Hannet, F. I.; Zeiss, R., and Terwilliger, E. H.: Results of Stimulation of Tegmentum with Horsley-Clarke Stereotaxic Apparatus, Arch. Neurol. & Psychiat. **28**:513 (Sept.) 1932.

EXPERIMENTAL "ENCEPHALITIS" PRODUCED BY INTRAVENOUS INJECTION OF VARIOUS COAGULANTS

PAUL F. A. HOEFER, M.D.*

TRACY J. PUTNAM, M.D.

AND

MILDRED G. GRAY, M.A.

BOSTON

Recent studies have shown that lesions closely resembling those of "encephalomyelitis" (and at a later stage of development those of multiple sclerosis) may be produced by experimental obstruction of cerebral venules [1] and may be observed in human pathologic material after thrombosis or sclerosis of small veins or, less often, of arteries under certain conditions.[2] Thrombi are common in the early stages of "encephalomyelitis" of certain types (e. g., those following measles and vaccinia).[3] The onset of such "encephalomyelitides" usually corresponds closely with the first establishment of an immunity to the antecedent disease.[4] An abnormal lability of the coagulation mechanism may be demonstrated in many cases of multiple sclerosis.[5]

It is reasonable to suppose, therefore, that experimentally produced hypercoagulability of the blood might in some instances result in throm-

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* Holder of grants from the Rockefeller Foundation and the Emergency Committee in Aid of Displaced Foreign Physicians.

Read at the Sixty-Third Annual Meeting of the American Neurological Association, Atlantic City, June 4, 1937.

From the Department of Neurology, the Harvard University Medical School, and the Neurologic Unit, the Boston City Hospital.

The expenses of the technical work were defrayed in part by a grant from Child Neurology Research (the Friedsam Foundation).

1. Putnam, T. J.: "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929 (May) 1935.

2. Alexander, L., and Putnam, T. J. : To be published.

3. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis, Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

4. Finley, K. H.: The Pathogenesis of Encephalitis Occurring with Vaccinia, Variola and Measles, Arch. Neurol. & Psychiat., to be published.

5. Simon, B., and Solomon, P.: Multiple Sclerosis: Effect of Typhoid Vaccine and of Epinephrine on Coagulation of Blood, Arch. Neurol. & Psychiat. **34**: 1286 (Dec.) 1935.

bosis of cerebral vessels, and in parenchymal lesions of an "encephalitic" type. The present study was undertaken to observe what changes, if any, in the central nervous system result from hypercoagulability of the blood produced experimentally. Kusama [6] and others provoked diffuse thrombosis in experimental animals by the intravenous injection of a great variety of substances, including organ extracts, homologous and heterologous serums, bacterial suspensions and extracts, colloid suspensions, lipoid solvents and the salts of heavy metals. Lesions were most commonly observed in the liver, lungs and kidneys. Although paralyses and convulsions were often mentioned, apparently little attention was paid to the possible presence of thrombi in the brain and their late results.

PRODUCTION OF ACUTE THROMBOSIS IN CEREBRAL VESSELS

One group of experiments consisted in an attempt to produce acute diffuse thrombosis for the purpose of studying cerebral thrombi. Following, in part, Kusama's earlier experiments we employed a number of coagulants. They were: homologous serum, heterologous serum (human serum in dogs; dog serum in rabbits) and standard typhoid vaccine containing 2,500,000,000 killed organisms per cubic centimeter. All these produced generalized thrombosis and death within from a few minutes up to half an hour when administered intravenously in doses of from 1 to 2 cc. At autopsy were observed firm, gross thrombi in the heart, the meningeal vessels and the vessels of the base of the brain and microscopic thrombi in the heart, liver, lungs and brain, the only organs examined (fig. 1). The thrombi were distinguished grossly and microscopically by the fact that they distended the vessel in which they lay. They consisted of masses of red cells containing clumps of platelets and often leukocytes, bound together by a meshwork of fibrin. The whole structure often appeared brittle (fig. 2). In general, thrombi were far less numerous in the brain than in other organs, and in several instances it was difficult to be sure that any were present.

In addition, Mills' lung extract was tried, as it was recommended by Pickering [7] as a reliable coagulant. It appeared the most suitable for our purpose of all the substances employed, as the fatal dose is fairly uniform for each lot. The distribution of the thrombi produced

6. Kusama, S.: Ueber Aufbau und Entstehung der toxischen Thrombose und deren Bedeutung, Beitr. z. path. Anat. u. z. allg. Path. **55**:459, 1913.

7. Pickering, J. W.: The Blood Plasma in Health and Disease, New York, The Macmillan Company, 1928. Mills, C. A.: Chemical Nature of Tissue Coagulins, J. Biol. Chem. **46**:135, 1921.

was essentially as already described. In their structure precipitation of fibrin was prominent, though agglutination of platelets also occurred (fig. 2).

Since Rivers and Schwentker [8] described "disseminated encephalomyelitis" produced by injection of brain extract, a material prepared

Fig. 1.—Gross thrombus in the heart of a rabbit which died three minutes after intravenous injection of lung extract.

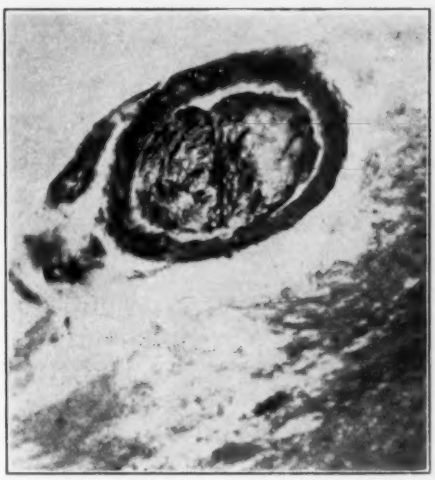

Fig. 2.—Fibrinous thrombus from a cerebral vessel of the same rabbit as that dying three minutes after injection of lung extract. Note the distention of the vessel, the densely packed cells and the brittle framework of fibrin. Mallory's connective tissue stain; 8 mm. lens.

8. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction, Experimentally Produced in Monkeys, J. Exper. Med. **61**:689, 1935.

according to their method was tested for its coagulant properties. It proved to be effective in causing generalized intravascular clotting (fig. 3).

In an attempt to determine which proteins of the blood are chiefly concerned with the induction of clotting, human plasma was precipitated fractionally by the addition of successive increments of neutral sodium phosphate, according to the methods described by Pickering,[7] into fairly uniform solutions of fibrinogen, "total globulin," euglobulin, pseudoglobulin (two fractions) and albumin. In addition, a suspension of

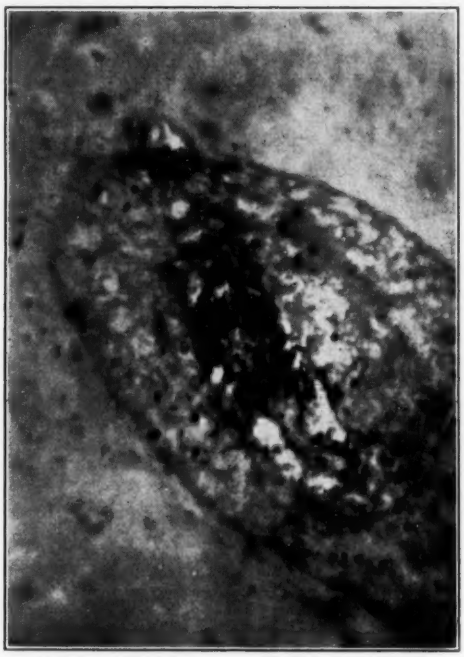

Fig. 3.—Fibrinous thrombus in a cerebral vein, from a cat which died five minutes after intravenous injection of a brain extract prepared according to the method of Rivers and Schwentker.[8] Notice the distention of the vessel, the adherence of the fibrin network to the walls and the masses of platelets. Mallory's connective tissue stain; oil immersion lens.

platelets was prepared. Each fraction was injected into several animals, in amounts corresponding to the fatal dose of heterologous serum. The fibrinogen, "total globulin," euglobulin and pseudoglobulin fractions produced gross and microscopic intravascular clots, while the suspension of platelets and the solution of albumin did not.

To determine more accurately the location of thrombi, india ink was injected with the coagulant in four instances. Under normal circum-

stances ink is swept cleanly out of the vessels of the brain and heart and gathered in the lungs, liver and bone marrow, but in all these experiments particles of carbon enmeshed in fibrin could be demonstrated in gross clots in the heart and in cerebral vessels.

In all, twenty-seven acute experiments with two cats, four dogs and twenty-one rabbits were performed, with the use of eight different coagulants. The results are shown in table 1.

A typical protocol of an acute experiment follows:

A new lung extract,[9] prepared on Oct. 21, 1936, was injected on October 22 into a rabbit weighing 2 Kg.

2:59 p. m.: Injection of 2 cc. slowly into an ear vein.

3: p. m.: Very severe generalized convulsions.

3:01½ p. m.: Death.

Autopsy was performed immediately; the chest was opened first. There were: thrombosis of the right side of the heart, extending into the major vessels (fig. 1);

TABLE 1.—*Materials and Animals Used in Experiments Terminating in Acute Fatal Thrombosis*

Coagulants	Rabbits	Dogs	Cats
Dog serum	3	..	..
Lung extract	13	4	2
Fibrinogen	1	..	..
Globulin suspension	2	..	..
Albumin suspension	1	..	..
Rivers' extract	1	..	1

thrombosis of both main vessels of the lungs, and thrombosis of the major vessels of the brain, all the vessels being markedly filled. The liver was grossly normal.

Microscopic Examination.—Thrombi of a uniform type were observed in the organs examined (heart, liver, lungs and brain). They were most extensive in the heart and were characterized by coral-like strands of agglutinated platelets, enmeshing leukocytes, from which a network of fibrin radiated. They were least obvious in the brain, but in occasional cerebral and meningeal vessels structures similar in miniature to those in other organs distended the vessel.

LATE LESIONS RESULTING FROM CEREBRAL THROMBOSIS

In a group of thirty-four animals sublethal doses of coagulants were administered, either on one occasion or repeatedly, and the animals were permitted to survive long enough for parenchymal changes to occur. Several of them showed neurologic symptoms, such as blindness, nystagmus, incoordination and paraplegia. The duration of the various experiments, the animals used and the materials employed are listed in table 2.

9. The potency of the different lung extracts varied. Therefore, amounts given in different series of experiments cannot be compared immediately.

Definite structural alterations were observed in twenty-two animals, although lesions of the central nervous system were seen in only thirteen.[10] In twelve other chronic experiments no lesions were demonstrated. The experiments lasted from two to one hundred and ninety-seven days.

In two chronic experiments the intense congestion of veins in the white matter, characteristic of human "encephalitides," was seen without local cellular lesions (fig. 4). Proliferative lesions were observed elsewhere, however, in both instances. The mildest cellular lesion was proliferation of oligodendroglia cells about a thrombosed vein near the lateral ventricle, in a dog given homologous serum for two days (fig. 5). The lesions in most of the other animals were somewhat more numerous in the white matter than in the gray, and occurred slightly more often in the brain stem and cerebellum than in the hemispheres. The commonest

TABLE 2.—*Summary of Twenty-Two Chronic Experiments Giving Positive Results*

Material Injected	Species		
	Rabbit	Cat	Dog
Typhoid vaccine	1*	..	..
Dog serum	1*	..	2*
Extract of lung	1*	6* (2+)	1†
Extract of brain	1†	..	..
Globulin fractions	1* (1+)	..	..
Shwartzman bacterial filtrate	..	1*‡ (4+)	..

* Lesions were observed in the brain.
† Lesions were observed only in organs other than the brain.
‡ A meningococcus filtrate was used.

lesions were dense perivenous cuffs, composed chiefly of microglia cells with a few cells resembling lymphocytes and plasma cells (fig. 6). Some of the phagocytes contained fat or myelin droplets. The next most common lesions were areas of diffuse astrocytic proliferation (fig. 7 *A*), and these usually corresponded to small perivascular lesions of myelin (fig. 7 *B*), in which axis-cylinders were left essentially intact and nerve cells suffered but little. One such area was seen in an animal which had survived the original injection sixteen weeks; in it was early, dense glial fibrosis (fig. 8 *A*). When focal lesions occurred in the cortex, they led to a circumscribed anemic change in the adjacent ganglion cells, with satellitosis (fig. 8 *B*). The most intense changes were seen in the brain of a cat described in the protocol which follows. No actual necroses or cysts of softening occurred.

10. Lesions of the central nervous system were observed in 36.5 per cent of all animals examined, while they were present in about 59 per cent of the animals showing lesions anywhere (table 2).

The significance of such lesions in rabbits may well be questioned. Similar lesions occurring spontaneously have been observed in only two of several hundred dogs on which autopsy was done in this laboratory, and they have rarely been reported by other investigators. As far as we are aware, they have never been observed in cats.

The protocol of a representative chronic experiment is given.

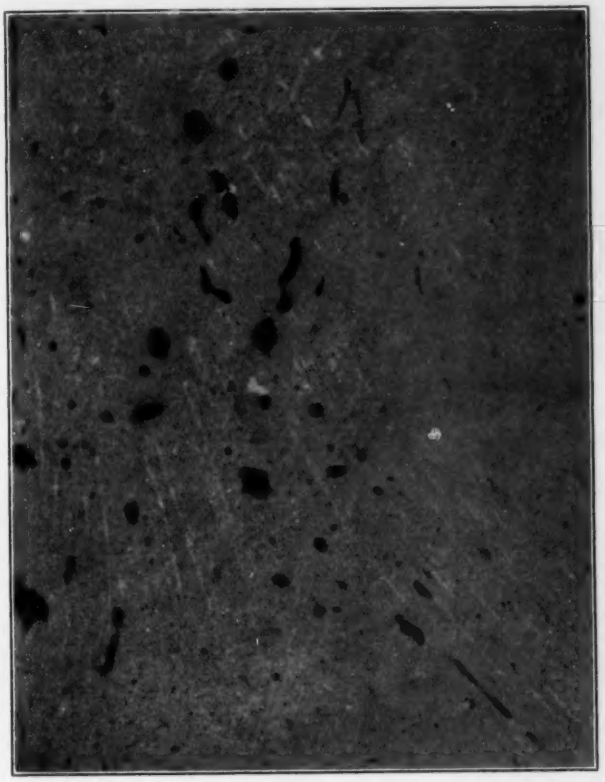

Fig. 4.—Distended (and thrombosed?) veins in the white matter of the hemisphere of a cat which was given lung extract for two weeks. Although there is no definite cellular reaction locally, infiltrations were observed in other sections. Mallory's connective tissue stain; lens enlargement.

Mills' lung extract, prepared on Oct. 14, 1936, was injected into a female cat, weighing 2.49 Kg.

October 15:

10: 54 a. m.: Ether anesthesia started.
10: 57 a. m.: Animal tied down; kept under light anesthesia.
11: 22 a. m.: Injection of 1 cc. of extract into right femoral vein.
11: 33 a. m.: Cat returned to cage; stands.
2: 30 p. m.: Cat well.

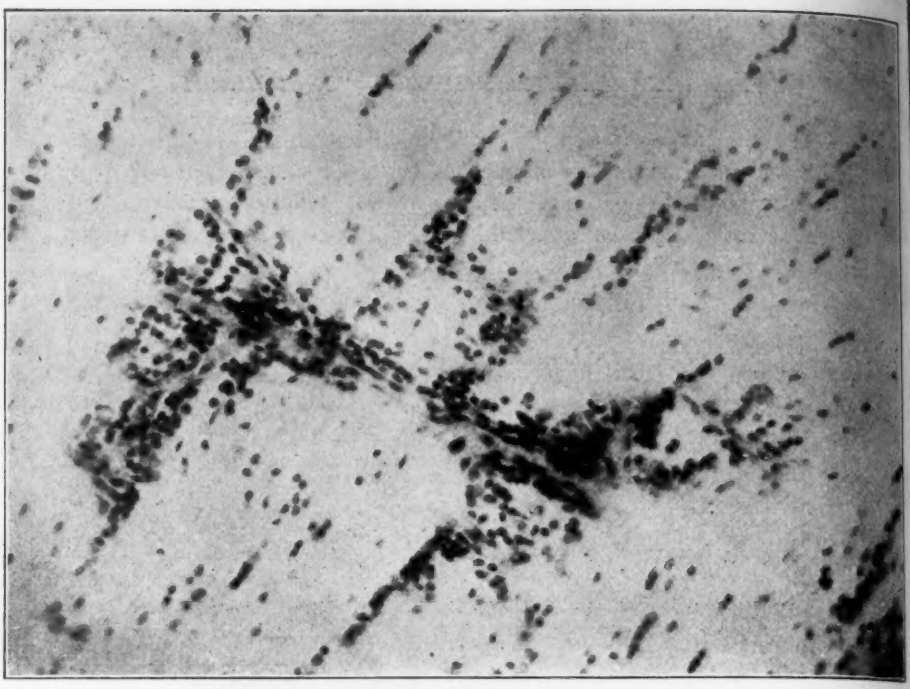

Fig. 5.—Proliferation of oligodendroglia cells about a thrombosed vein near the lateral ventricle, from the brain of a dog killed four days after intravenous injection of 85 cc. of a homologous serum, given in two doses. Giemsa stain; 8 mm. lens.

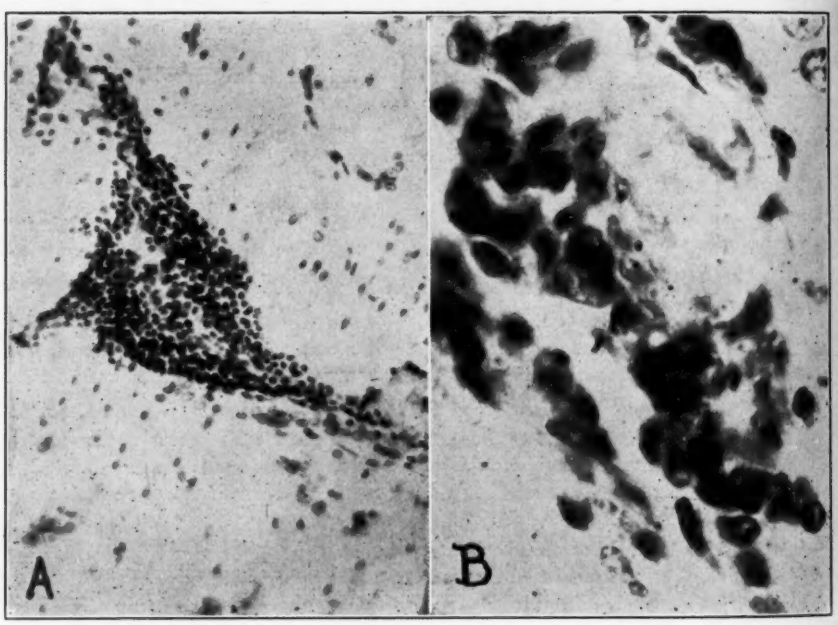

Fig. 6.—*A*, cuffing of a subependymal vein by an intra-adventitial accumulation of microglia cells and cells resembling lymphocytes and plasma cells, from the brain of a cat given an intravenous injection of lung extract four days previously. Gallocyanine stain; 16 mm. lens. *B*, infiltrating cells seen under an oil immersion lens, from the same slide as that shown in *A*.

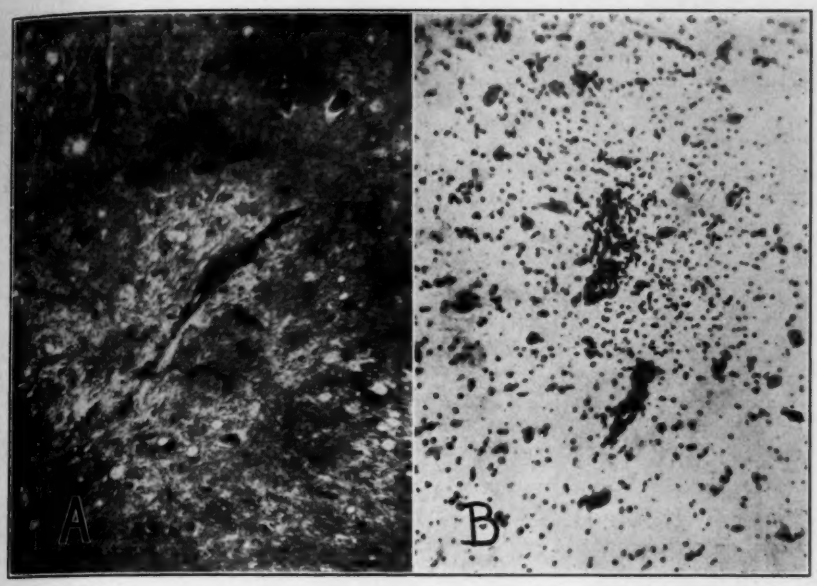

Fig. 7.—*A*, area of demyelination in the white matter of the cerebellum from a cat which had been given a single dose of lung extract together with an anticoagulant (cysteine) four days previously. Mallory's connective tissue stain; 16 mm. lens. *B*, section adjacent to that in *A*, showing diffuse proliferation of glia cells about the same vessel. Gallocyanine stain; 16 mm. lens.

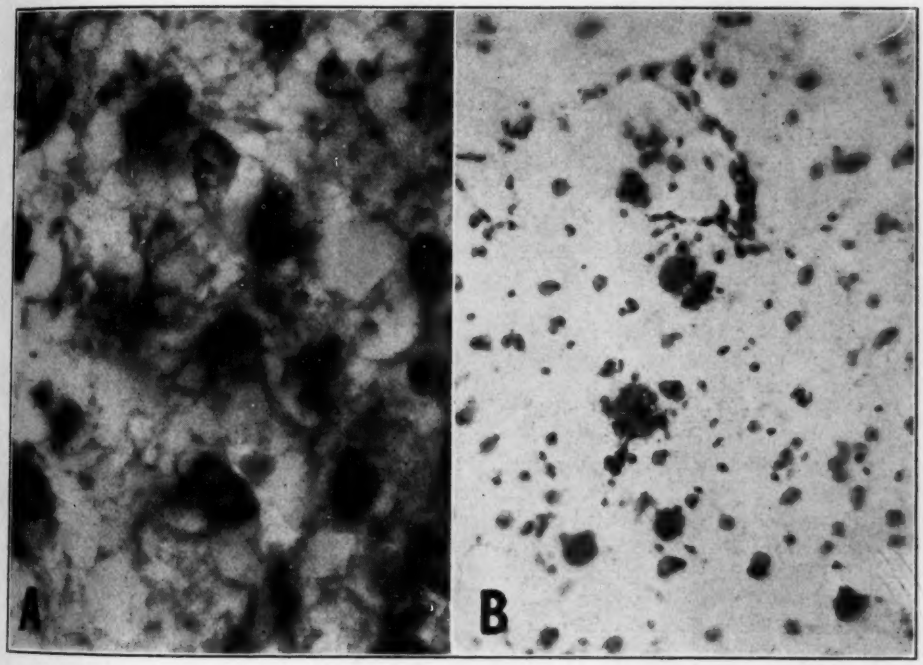

Fig. 8.—*A*, glial fibrosis in a degenerated area in the lenticular nucleus of a cat given three injections of lung extract in one week and allowed to survive nineteen weeks. Phosphotungstic acid-hematoxylin stain; oil immersion. *B*, satellitosis in a cortical focus, from the brain of a young dog given 205 cc. of homologous serum intravenously in divided doses over fifty days and then allowed to survive forty days. Gallocyanine stain; 8 mm. lens.

October 16: Cat normal.

1:15 p. m.: Animal etherized and tied down.

1:24 p. m.: Injection of 2 cc. of extract into left femoral vein.

1:26 p. m.: Respiration stops; short, jerky respiration; heart action good; artificial respiration.

1:29 p. m.: Respiration starts again.

1:34 p. m.: Respiration good; cat returned to cage.

1:50 p. m.: Respiration good; deep sleep.

2:12 p. m.: Respiration good; deep sleep.

October 17: 9:30 a. m.: Cat awake and crying; both hindlegs paretic; crawls on forelegs, is able to stand for a short time if placed on all four legs but not spontaneously; will not eat.

October 18: 2:30 p. m.: Cat very weak.

October 19: Cat still very weak. Sitting or lying in cage; crying; no gross elevation of temperature. Will not eat. Hindlegs paretic; forelegs weak. Head droops. Animal unable to jump. When placed outside cage cat starts crawling slowly in a circle, always toward the right. Does not mind dogs. Possibility of blindness. Examination with flashlight shows that pupils are equal and react equally to light. Does not evade the strong light as other cats do. Does not see obstacles in way, dogs, etc.

Oct. 20 (a. m.): Cat did not eat spontaneously during the preceding two days; was given milk by mouth through tube. This morning cat presents the following motor phenomenon: From whatever position she is brought, she rolls over on her back and moves forelegs and left hindleg rhythmically. Respiration quick and somewhat stertorous. No signs of light perception. Temperature 40 C. at 10 a. m. About 11 a. m. 25 cc. of milk was fed, whereon the cat vomited, at about 11:10 a. m. A short violent period of convulsions started, lasting a few minutes, and the cat died, five days after onset of symptoms.

Comment.—The clinical symptoms indicated: (1) blindness with persistent pupillary reactions; (2) deviation of gait to right; (3) paraplegia of both hindlegs and possibly of the right foreleg. The brain should show several distinct lesions.

Autopsy (performed immediately).—After the calvarium was lifted, a fresh red, hemorrhage was observed in the region of both occipital poles, below the dura. It could not be wiped away and extended along the lower surface of the occipital lobe. There was a clotted vessel in the falx cerebri, and the left temporoparietal lobe showed one large and two small old, brownish foci of hemorrhage. The heart was small, in systolic contracture and empty. There were no clots in the heart or large vessels. The middle and lower lobes of the right lung showed several irregular, dark brownish areas. The question of infarct or bronchopneumonic spots arose. The liver was grossly normal.

Sections were taken from both hemispheres and the brain stem. All sections from the hemispheres showed a widespread, intense degenerative, reparative and exudative process, involving both the gray and the white matter, but perhaps on the whole more particularly the latter (fig. 9). The degeneration affected chiefly the nerve cells and myelin (fig. 10*A*). Persistent axis-cylinders were seen in sections stained by Bodian's method (fig. 10*B*). The infiltrative changes were most intense about veins and venules, many of which were thrombosed and necrotic. They could be divided into two types: diffuse proliferation of "fixed" glial elements, especially astrocytes, predominating in the white matter (fig. 5), and

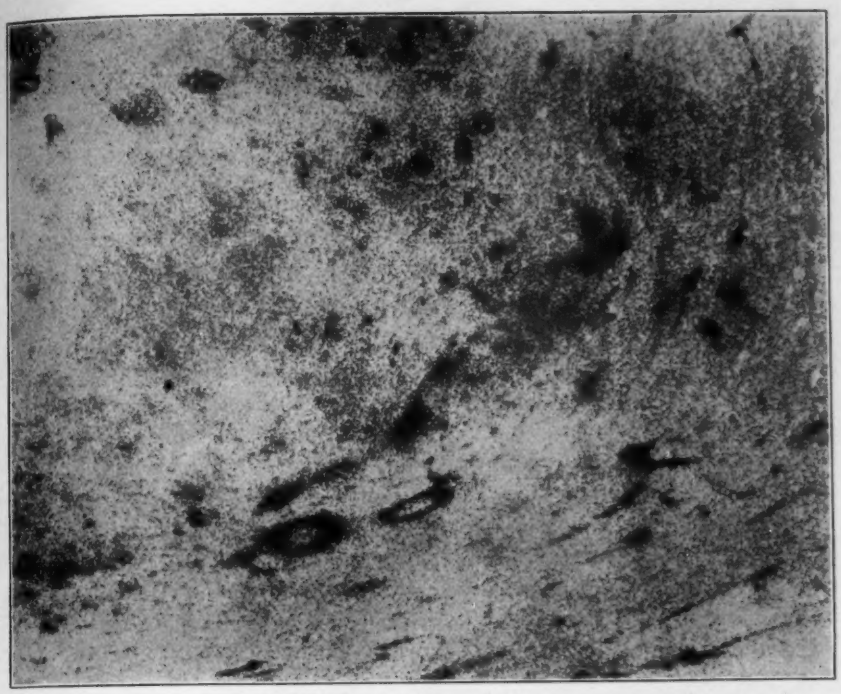

Fig. 9.—"Necrotizing encephalomyelitis" in the brain of a cat which was given sublethal doses of lung extract for two days in succession and then allowed to survive five days. Gallocyanine stain; lens enlargement.

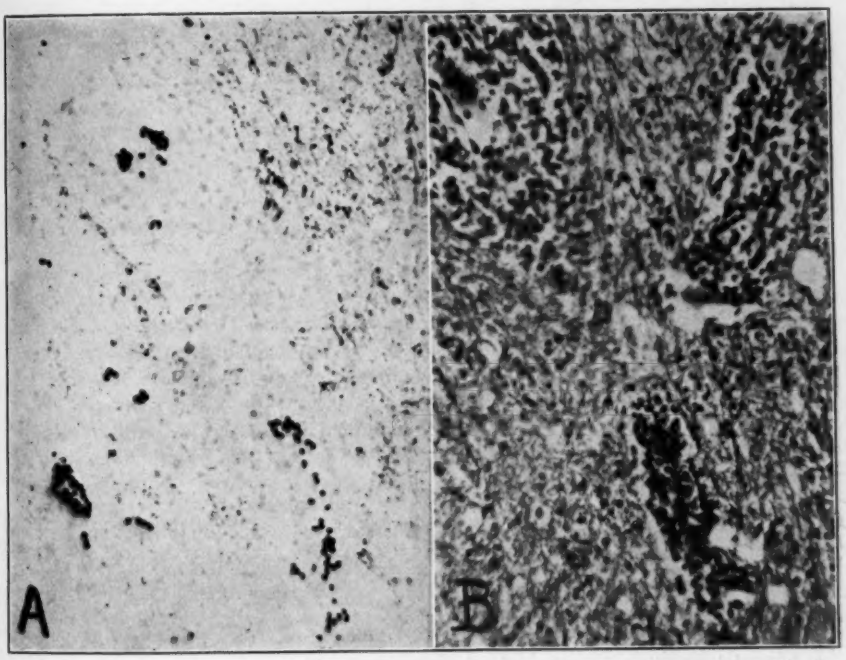

Fig. 10.—*A*, demyelination about three infiltrated vessels, from the same block as that illustrated in figure 9. Mahon's myelin stain; 8 mm. lens. *B*, relative persistence of axis-cylinders about the three vessels shown in *A*. Bodian axis-cylinder stain; 8 mm. lens.

accumulation of cells within the adventitia of vessels. Most of the cells were obviously microglia cells, but others resembling lymphocytes and plasma cells occurred (fig. 6). There was moderate infiltration of the meninges.

INHIBITION OF CLOTTING BY USE OF ANTICOAGULANTS

The possibility suggested itself that acute death or the formation of chronic lesions as a result of administration of coagulant substances might be prevented by the use of anticoagulants. Heparin proved capable of preventing acute death from administration of five times the dose of lung extract, but its effect was transient. Cysteine,[11] germanin[12] and Evan's blue[13] proved more convenient and reliable. Moreover, their activity lasts at least for several days. Altogether, nineteen cats and one rabbit were protected against usually fatal doses of lung extract by heparin (four animals) cysteine given by mouth and intravenously (eight animals), germanin (five animals), Evans' blue, taurocholate and glycocholate (one animal each).

This series of experiments, which might conceivably have a practical application, is still in progress.

SUMMARY

1. Coagulant agents of many types when injected into the circulation are capable of producing thrombi in the central nervous system, as well as in other organs.

2. In chronic experiments the cerebral lesions closely resemble those of certain human "encephalomyelitides," for example, those of the postvaccinal and postmeasles types.

3. In some instances acute death from massive doses of coagulants may be prevented by the previous administration of an anticoagulant.

DISCUSSION

DR. JOSEPH H. GLOBUS, New York: I read this paper with great pleasure and was impressed with the method of approach and the results of the study. The question of the etiology of multiple sclerosis is in a state of great confusion, particularly in view of the close similarity of the character and distribution of the lesions to those observed in so-called meningo-encephalomyelitis. It becomes imperative to attack the problem in a new way and by new means. This is exactly what these workers have done. While it must be admitted that they are still far from solving the problem of the etiology of multiple sclerosis, they have initiated a new method; they have turned a new page. It is a good beginning.

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11. Sterner, J. H., and Medes, G.: The Effect of Certain Sulphur Compounds on the Coagulation of Blood, Proc. Soc. Exper. Biol. & Med. **34**:575, 1936.

12. Stuber, B., and Lang, K.: Zur Pathogenese und Therapie der Thrombose, Klin. Wchnschr. **9**:1113, 1930.

13. Gibson, J. R., and Evans, W. A.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Investigation **11**:301, 1937.

I have examined some of the preparations, as well as some of the photomicrographs, and cannot help but be impressed with the character of the lesions produced by this new experimental method; they closely resemble those seen in disseminated meningomyelitis and so-called acute multiple sclerosis. All that one can say for the present, on the basis of the data at hand, is that coagulant agents are capable of producing lesions in the nervous system which are similar to those of acute multiple sclerosis and meningomyelitis. Not without interest is also the established fact that these lesions can be aborted by administration of anticoagulants. Thus, such results, and, above all, the new method of approach to the problems, deserve unstinted praise.

DR. ARTHUR WEIL, Chicago: For many years I have followed with great interest the work of Dr. Putnam and his associates in trying to reproduce experimentally the human disease multiple sclerosis in animals: first, the attempt to repeat their observations in dogs in which injection of tetanus toxin produced demyelination and, more recently, their demonstration that multiple venous thrombosis may produce disseminated demyelination. But the question arises whether the pictures which they have demonstrated here are in any way related to the human disease multiple sclerosis.

One has to ask: Granted that the theory is right, what would one expect first in the human brain after formation of multiple venous thrombi? Of course, one would expect first to see the thrombi in acute plaques and, if they remain in the human brain for any length of time, organization or final canalization. One would also expect to see permanent scars, following these multiple vascular insults. I tried to convince myself of the presence of such vascular lesions. Last year I studied the material of Marburg, that of Dr. I. Bertrand and my own, always with the point in view of detecting such remains of vascular obstruction. But I could not convince myself that I saw any sequelae of thrombosis, such as organization, vascularization or canalization of the thrombi. Of course, one may find acute thrombi caused by stasis following impairment of circulation, which one may observe in the final stages of any disease, but one does not see older organized thrombi as a regular occurrence in multiple sclerosis.

The second question is: Granted that such multiple vascular lesions are the basis of the pathologic change in multiple sclerosis, do the human preparations indicate such a relation of plaques to vascular distribution? It is known from the work of Marburg and his pupils, who made serial sections of plaques and reconstructed them, that the plaques have no relationship to the vascular tree. It is known from the work of Steiner that the region which is most susceptible to the pathologic activity of multiple sclerosis is the lining of the lateral ventricles and the subependymal tissue and that from this *Wetterwinkel* the demyelination spreads into the surrounding tissue. One has, therefore, no basis for the conclusion that these experiments reproduce multiple sclerosis. These experimental lesions are connected with the distribution of vascular channels. In multiple sclerosis one is dealing with a chronic disease, with exacerbations and remissions. In order to satisfy the theory, one has to assume that from time to time thrombi are formed, which are dissolved again after a short time and leave no trace of their existence.

If such a short interruption of blood supply is assumed, one cannot visualize why merely the myelin sheaths of the white matter should be attacked and neurons, which are many times as sensitive to interruption of blood supply, should be spared. In the preparations in which venous thrombi had formed in the gray matter, the neurons in the vicinity of these small blood vessels were as severely affected as were the myelin sheaths. One cannot understand why the axis-cylinders

should be spared by such a process, even by short anoxemia. Interesting as the experiments may be, in opening a new field of investigation one has to be careful in drawing any conclusion on this basis as to the etiology of the human disease multiple sclerosis.

DR. TRACY PUTNAM: Dr. Hoefer and I did not wish particularly to enter the field of multiple sclerosis at this time. We are presenting not a theory but experimental results. However, I may say that the points which Dr. Weil so ably brings up have occurred to us also, and I will briefly discuss some of them.

First, we also have examined with some care the site of the thrombi in cases of multiple sclerosis. This is not as simple as it may seem. The preparations stained by the ordinary neuropathologic technics are peculiarly adapted to conceal any thrombi which may exist. They can be seen only with specially adapted stains, such as the Masson, or possibly the Mallory, stain. If these are used, thrombi will be seen in a large proportion of cases of encephalitis and in a certain proportion of cases of multiple sclerosis. Moreover, one can observe evidences of vascular occlusion other than thrombi in cases of multiple sclerosis, such as closure of vessels, perivascular accumulation of pigment and enormous passive dilatation—far greater than one ever sees in an active inflammatory area.

Our reconstructions show that these plaques surround veins like a sleeve, as reported by Dawson, Wohlwill and Faliewicz. This was obvious in our own reconstructions, which were a little more elaborate than those previously described, and it was obvious that new plaques formed around new thrombi.

With regard to the preferential destruction of myelin: These particular experiments are not well adapted to bring out this fact, for they have been too brief. The experiments, however, which produced mechanical destruction of cerebral venules, which I reported before this association several years ago, showed exquisite destruction of myelin with complete retention of axis-cylinders, and this is precisely what Dr. Leo Alexander and I have seen after spontaneous venous thromboses in human beings. However, as I say, this observation is a little beside the point of the present paper.

In encephalitis, of the acute postinfectious type, in general one can easily see thrombi, and they have been reported by the majority of authors. I believe that the congestion following the thrombosis has been uniformly reported by those who have studied these lesions in their acute stages.

Case Reports

SUBARACHNOID HEMORRHAGE DURING SHOCK THERAPY FOR SCHIZOPHRENIA

HERBERT FREED, M.D., AND CHARLES W. WOFFORD, M.D., PHILADELPHIA

This case of subarachnoid hemorrhage occurring during insulin shock treatment for dementia praecox is reported because a similar case has not been found in the literature; Sakel [1] also stated that he had not encountered such a condition.

R. B., a white man aged 30, was admitted to the Philadelphia General Hospital on Dec. 18, 1936, with a history typical of acute onset of a schizophrenic episode of catatonic type. Insulin shock therapy was started on Jan. 8, 1937. The patient received 75 units of insulin at 7:30 a. m. on January 22; at 11 a. m. he passed into coma. He slept quietly, with regular respirations and no convulsive movements until 1 p. m., when 50 Gm. of Karo syrup was given by nasal tube to terminate the coma. No response occurred in forty minutes; 55 Gm. of dextrose was given intravenously in the course of the next hour. Muscular rigidity, which had appeared before injection of the last dose of dextrose, became pronounced and generalized. At 3 p. m. the patient presented opisthotonos, without the clonic movements characteristic of the ordinary type of convulsion. The arms were generally flexed; the eyeballs moved constantly, usually upward and to the left. The pupils showed hippus, but were generally dilated and did not respond to light. Sweating and stertorous respiration, with moderate cyanosis, continued throughout this period. At 3:45 p. m. a spinal tap showed bloody spinal fluid, with a normal pressure of 9 mm. of mercury. In the course of this episode the temperature rose from 99 (axillary) to 104 F. (rectal); the pulse rate varied from 80 to 150 a minute, and the respiratory rate rose to 60 as the lungs became edematous.

Treatment consisted of intravenous injection of large doses of atropine and calcium chloride and intravenous and intramuscular injections of soluble phenobarbital, together with parenteral administration of dextrose and measures, such as alcohol sponges, designed to reduce the temperature. The alarming symptoms gradually subsided as the treatment was instituted, but the patient remained comatose. The temperature and the pulse and respiratory rates remained elevated during the course of the next eighteen hours; the blood pressure varied from 130 systolic and 85 diastolic to 105 systolic and 75 diastolic. The blood sugar was 380 mg. per hundred cubic centimeters.

On the next day, at 9 a. m., the sugar content of the blood was 130 mg.; the urea content, 16 mg.; the carbon dioxide combining power, 56 cc., and the blood pressure, 97 systolic and 85 diastolic. Neurologic examination revealed stupor,

From the insulin shock therapy ward, by permission of Dr. Baldwin F. Keyes.

Read at the Sixty-Third Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 3, 1937.

1. Sakel, M.: Personal communication to the authors.

with moderate contraction of the pupils, which were round and regular and reacted sluggishly to light. Painful pressure caused bilateral contraction of the facial muscles. The left arm showed slight increase in tonus, with a suggestion of weakness as compared with the right. The left leg showed diminution of power on involuntary movements, without increase in tonus. The deep reflexes were equal in the two arms, but were absent in the left leg. There was an inconstant Babinski sign on the left. There was definite nuchal rigidity, with a Kernig sign bilaterally.

Two days later the patient was still semistuporous, but the only evidences of involvement of the central nervous system were a Kernig sign and nuchal rigidity. On January 28, six days after the onset, the spinal fluid was still grossly bloody, with no increase in pressure. During the course of the next three weeks the patient passed through an active psychotic episode, during which he was noisy, with thickened speech, and apparently voluntarily incontinent at times. By February 28 he had improved to such a degree that he was ready for discharge. He had acquired insight into the psychotic episode. Neurologic examination revealed that the cranial nerves were normal. The ocular fundi were normal except for slight blurring on the nasal side of the disks. (It should be noted that good power was not present in the facial muscles on voluntary innervation and that there was some external deviation of the left eye; however, both these symptoms had been present before the institution of insulin shock treatment.) The deep reflexes were about equal and of normal strength in the two arms; they were increased in both legs, more so in the left. There was no clonus. The Babinski sign was not elicited on the right and was variable on the left, being doubtful or present at different times. The Oppenheim sign was present on the right. The abdominal reflexes were diminished but present in the upper portion of the abdomen and absent in the lower. The cremasteric reflexes were not obtained. No nuchal rigidity or Kernig sign was present. The mental status of the patient at this time was good; there were no delusions or hallucinations, and the affect and insight were normal.

On the basis of the neurologic findings, a diagnosis of subarachnoid hemorrhage occurring during insulin shock therapy was made.

The patient has been seen in the outpatient department since his discharge from the hospital; his status is unchanged.

COMMENT

The literature contains reports of various types of hemorrhage associated with hypoglycemia. Ehrmann and Jacoby [2] reported two cases of hemorrhage in the lungs and brain after insulin therapy. Both patients were in coma, and insulin had no effect until just before death, when the blood sugar reached 0.04 mg. per hundred cubic centimeters. Moreover, both had parenchymatous nephritis, and one, hemorrhage into the stomach and trachea. Therefore, as the authors stated, there was already a previous injury to the blood vessels. While one cannot exclude the possibility of insulin serving as a contributing factor, at least, in the production of hemorrhages, the likelihood that it plays a direct, specific role is in doubt.

2. Ehrmann, R., and Jacoby, A.: Hemorrhages After Insulin Treatment, Deutsche med. Wchnschr. **50**:138, 1924.

Güdemann [3] and Henderson [4] reported five cases of hematuria, and Güdemann also described two cases of melena following administration of insulin. Two of five patients were in coma, and microscopic examination of the urine revealed blood cells, accompanied by casts and albumin —a not uncommon finding in diabetic coma. "Hematuria," therefore, loses somewhat its importance. No symptoms of hypoglycemia were present and no estimations of the blood sugar were reported, so that no conclusions can be drawn.

In six cases of spontaneous hypoglycemia at the Philadelphia General Hospital,[5] no gross hemorrhage into the viscera was reported postmortem, but microscopic perivascular hemorrhages were noted in the brain in all cases, and also in the stomach.

Baker and Lufkin [6] reported three cases in which the patients died of spontaneous hypoglycemia; numerous new and old hemorrhages were seen scattered irregularly throughout the brain. Hemorrhages seemed to be most numerous in the brains of patients who had had the most severe convulsive seizures. In most sections the size and distribution of the petechiae were such that no apparent injury was done to the surrounding tissue. With the red cells merely pushing the cerebral fibers apart, without causing rupture, little or no alteration in normal function would be expected. However, with severe convulsive seizures the resultant hemorrhages may become confluent and give rise to temporary or permanent neurologic manifestations.

In the case reported in this article, it must be admitted that one cannot rule out the occurrence of a spontaneous subarachnoid hemorrhage in a person with congenitally weakened vessels due to defects in the media resulting in aneurysmal dilatation of the cerebral vessels, as described by Forbus and Wolf.[7]

My colleagues and I have examined the eyegrounds of patients undergoing insulin shock therapy at intervals of from seven to ten days for evidence of hemorrhage or exudate, with the possibility in mind of a specific effect on the vascular system of insulin or hypoglycemia or both. We have not noted any lesions to date.

On the whole, we believe that the evidence strongly suggests, but does not prove, that there exists a causal relationship between hypoglycemia and hemorrhage into various organs. Several theories have been propounded for the physiologic action of hypoglycemia, one of which is that of anoxemia.[8] It has been established by Landis and

3. Güdemann, J.: Rare Complication of Insulin Treatment, Wien. klin. Wchnschr. **39**:963 (Aug. 19) 1926.

4. Henderson, J.: Haematuria Following Insulin Injections, Brit. M. J. **1**:231 (Feb. 5) 1927.

5. Riggs, H.: Personal communication to the authors.

6. Baker, A. B., and Lufkin, N. H.: Cerebral Lesions in Hypoglycemia, Arch. Path. **23**:190 (Feb.) 1937.

7. Forbus, W. D., and Wolf, F. S.: Amyotonia Congenita (Oppenheim's Disease) in Identical Twins, Bull. Johns Hopkins Hosp. **47**:309 (Dec.) 1930.

8. Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol. Rev. **14**:404 (July) 1934. Kleitman, N., and Magnus, R.: Pharmacology of the Body Righting and Labyrinthine Reflexes: XI. Action of Insulin on the Central Nervous System, Arch. f. d. ges. Physiol. **205**:148, 1924.

others [9] that anoxemia injures the walls of the capillaries resulting in increased permeability with diapedesis of red cells. This seems to be a plausible etiologic factor in our case.

CONCLUSION

A case of subarachnoid hemorrhage with recovery occurring during the course of insulin shock treatment is reported.

9. Olmsted, J. M. D., and Logan, H. D.: Effect of Insulin on Central Nervous System and Its Relation to Pituitary Body, Am. J. Physiol. **66**:437 (Oct.) 1929. Footnote 8.

News and Comment

CELEBRATION IN HONOR OF DR. SMITH ELY JELLIFFE

The thirty-fifth anniversary of Dr. Smith Ely Jelliffe's editorship of the *Journal of Nervous and Mental Diseases* will be celebrated at the New York Academy of Medicine on April 22, 1938. The celebration will consist of a symposium on neuropsychiatry, to be held at 2 p. m., and will be followed in the evening by a dinner.

The speakers at the afternoon session will include Drs. Adolf Meyer, Earl D. Bond, George Draper, Frederick Tilney, Oskar Diethelm and Karl Menninger. Dr. Foster Kennedy will act as toastmaster at the banquet. Drs. A. A. Brill, Louis Casamajor, Henry Alsop Riley and Richard H. Hutchings will speak of the activities of Dr. Jelliffe as a psychiatrist and psychoanalyst, as a man, as a neurologist and as a bibliophile, respectively.

THOMAS WILLIAM SALMON MEMORIAL LECTURES

The sixth series of the Thomas William Salmon Memorial Lectures will be given by Dr. David Kennedy Henderson, physician superintendent of the Royal Edinburgh Hospital for Mental Disorders, Edinburgh, Scotland, on April 18, 19 and 20, 1938, at 8:30 p. m., at the New York Academy of Medicine, 2 East One Hundred and Third Street, New York. The subject of the lectures is psychopathic states, considered from the standpoint of (1) their place in psychiatry; (2) their characteristics, as evidenced by (*A*) aggression, (*B*) inadequacy and (*C*) creativeness, and (3) their understanding and synthesis.

The lectures are open to all physicians and their friends who are interested in psychiatry.

Abstracts from Current Literature

Anatomy and Embryology

TRACTUS TECTO-SPINALIS IN THE CAT. A. T. RASMUSSEN, J. Comp. Neurol. **63**:501 (April) 1936.

This report is based on a study of nineteen Marchi series of brains of adult cats in which lesions of various sizes had been made in different parts of the lamina quadrigemina to determine the course of the tractus tectospinalis. In this species the tectospinal tract was observed to cross completely in the dorsal tegmental decussation. The tract arose solely from large cells in the superior colliculus. The fibers ended conspicuously about the motor nuclei of the lower region of the medulla oblongata and the ventral horn cells of the upper seven cervical segments of the spinal cord. No fibers were observed about the motor nuclei of the nerves to the muscles of the eye. Tectopontile and tectoreticular fibers were observed in abundance.

FRASER, Philadelphia.

SOME DETERMINATIONS OF THE RATIO OF NERVE FIBERS TO NERVE CELLS IN THE THORACIC DORSAL ROOTS AND GANGLIA OF THE CAT. DONALD DUNCAN and LESTER L. KEYSER, J. Comp. Neurol. **64**:303 (Aug.) 1936.

Investigators in Ranson's laboratory have found a ratio of dorsal root fibers to ganglion cells of 1:1. Other investigators have found an excess of cells. Duncan and Keyser make this report for the purpose of adding figures in support of the 1:1 ratio. Thoracic nerve fibers and ganglia of five healthy cats were counted. In twenty-one good preparations the ratio of fibers to cells ranged from 0.91 to 1.08. In the best preparations the number of axons exceeded the number of cells in the ganglion. Hence, Duncan and Keyser conclude that the number of nerve fibers in the thoracic dorsal root of the cat slightly exceeds the number of cells in the corresponding dorsal root ganglion. They suggest that in the material of investigators who observed fewer fibers than cells the finest fibers were not impregnated.

FRASER, Philadelphia.

A PHYLOGENETIC CONSIDERATION OF THE PRIMARY AND SECONDARY CENTERS AND CONNECTIONS OF THE TRIGEMINAL COMPLEX IN A SERIES OF VERTEBRATES. RUSSELL THOMAS WOODBURNE, J. Comp. Neurol. **65**:403 (Dec.) 1936.

In this study Woodburne considers the phylogenetic development of the trigeminal complex in a series of vertebrates, including representative forms of cyclostomes, ganoids, teleosts, amphibians, reptiles, birds and mammals. In cyclostomes only the motor nucleus and the nucleus of the descending root of the trigeminal nerve are represented. Some cells of the main sensory nucleus are seen in Amia, and this nucleus is particularly well developed in the brook trout. The nucleus of the mesencephalic root of the trigeminal nerve also appears first in Amia. Trigeminocerebellar connections, as well as cerebellomotor fibers to the nucleus of the trigeminal nerve, are seen in the cyclostomes. The nucleus of the descending root is small in urodeles. In birds the secondary fibers from the chief sensory nucleus and the nucleus of the descending root form the ascending system known as the trigeminal lemniscus. In all forms studied the entering sensory trigeminal fibers in part end at the plane of entrance and in part turn caudad as a descending root of the trigeminal nerve and become continuous with spinal tracts carrying similar impulses. Certain secondary connections of the sensory trigeminal complex, such as the internuclear connections with the motor nucleus of the trigeminal nerve, are represented in all forms. Crossed trigeminocerebellar connections are

supplemented in most forms by uncrossed fibers from the same area. Woodburne concludes that the trigeminal complex in its progressive development and differentiation typifies most clearly the progressive evolution of the nervous system and indicates how various levels develop simultaneously and in correlation with it.

ADDISON, Philadelphia.

CELLULAR MORPHOLOGY IN THE AREA POSTREMA. LESTER S. KING, J. Comp. Neurol. **66**:1 (Feb.) 1937.

King studied the area postrema in adult cats by means of Hortega silver methods. Strands of reticulin were observed between and around blood vessels. Neurons were not observed, but occasionally a single nerve fiber was seen coursing in this area. The intrinsic cells of the area were irregularly arranged, and resembled embryonic cells of the astroblastic series, of monopolar, bipolar and multipolar type. Only a few "sucker feet" were seen. The cells showed considerable fibrillar differentiation. King believes that cells of the area postrema are of adult type and peculiar morphologic character. ADDISON, Philadelphia.

THE ONTOGENETIC DEVELOPMENT OF THE DIENCEPHALIC CENTERS IN A BIRD'S BRAIN (CHICK) AND COMPARISON WITH THE REPTILIAN AND MAMMALIAN DIENCEPHALON. HARTWIG KUHLENBECK, J. Comp. Neurol. **66**:23 (Feb.) 1937.

The purpose of this study of the ontogenetic development of the diencephalic centers in a chick's brain was to contribute to knowledge of the fundamental morphologic pattern of the vertebrate diencephalon. Thirty series of embryonic chicks, from the 87 hour stage of incubation until hatching, were available. The first indication of the longitudinal zonal system appeared at the 87 hour stage. At the end of 97 hours the embryo showed the typical pattern of early diencephalic differentiation—epithalamus, thalamus dorsalis, thalamus ventralis and hypothalamus—and the corresponding sulci—sulcus diencephalicus dorsalis, sulcus parencephalicus and sulcus diencephalicus ventralis. Differentiation into cell masses was observed in an embryo of 120 hours. At the 12 day stage the fundamental differentiation of the nuclear pattern in all its definite form relations was considered complete, and further development involved only growth and internal structural details. The reptilian homologues of most avian diencephalic nuclei can be traced with a reasonable degree of certainty.

ADDISON, Philadelphia.

THE DEVELOPMENT OF VASCULARITY IN THE HINDBRAIN OF THE CHICK. R. G. WILLIAMS, J. Comp. Neurol. **66**:77 (Feb.) 1937.

The purpose of this study was to correlate the development of vascularity in the hindbrain of the chick with that of the finer structures which the vessels supply. The material consisted of a series of eight embryos, at stages of from 2 to 18 days, one newly hatched chick and the brain of a 2 year old hen. The blood vessels of all specimens were injected with dilute india ink. At the 48 hour stage of incubation a rich capillary plexus invested the hindbrain. From this plexus the basilar artery formed after the third day. The first point of entry of the capillary plexus was in the region of the fifth cranial nerve, at the 48 hour stage. After the third day the vessels had invaded the trigeminal ganglion. By the twelfth day the various motor nuclei in the hindbrain had reached their adult condition, except for size. The sensory nuclei appeared later than the motor, but it was not evident that this delay was associated with delayed vascularization. The state of the vessels in the brain of a 2 year old hen was about the same as that at hatching, except that some nuclei appeared to have a richer supply of vessels. No end-arteries were observed in the brain of the chick, but there was free anastomosis everywhere. The ratio of volume of brain substance to length of vessels in the brain had reached a constant at hatching. FRASER, Philadelphia.

A First Study of the Size of the Cells in the Cerebral Cortex. Gerhardt von Bonin, J. Comp. Neurol. **66**:103 (Feb.) 1937.

Von Bonin studied the size of the cells in the cerebral cortex as a basis for comparison of subhuman and human brains. Since the volume of the nucleus stands to that of the cell in a quadratic relation, the longest and shortest diameters of the nuclei were measured, and the volume computed by the formula $v = \frac{4}{3} \pi ab^2$, in which a and b represent the longest and the shortest diameter, respectively. By comparing the distribution curves for nuclear volume in different cortical areas, he showed a method for differentiation of areas.

Addison, Philadelphia.

Further Experimental Investigations on the Phenomenon of Homologous Response in Transplanted Amphibian Limbs: I. Functional Observations. Paul Weiss, J. Comp. Neurol. **66**:181 (Feb.) 1937.

Amblystoma mexicanum, a large, rapidly growing axolotl, was used for the transplantation of entire forelimbs. All experiments were done on free-swimming larvae, varying in length from 4 to 12 cm. Seventy-three experiments were successful. Transplants were always added to the left side of the host. In some cases the transplants were left limbs, either single or double; in others, right limbs, and in still others, limbs of different sizes. The transplants were applied at various angles. In all cases a controlled nerve supply, usually from the fifth spinal nerve, was assigned to the transplant. Circulation of blood was established in four days. A few weeks after the operation the muscles of the transplant resumed function. A detailed study of the sequence in which movements reappeared in the transplants revealed that the individual muscles took up function independently and without regard to the function of the transplant as a whole. Within two months all the muscles of the transplant had received innervation, and the transplant functioned exactly according to the rules of homologous response stated previously. Each muscle of the transplant contracted always at the same moment and with the same intensity as the synonymous muscle in the normal limb. All the described phenomena persisted after decerebration, from which Weiss concludes that the homologous response is due to some property inherent in the spinal mechanism rather than to the adjusting activities of cerebral centers.

Fraser, Philadelphia.

Visual Centers in Blinded Rats. Yü-Chüan Tsang, J. Comp. Neurol. **66**:211 (Feb.) 1937.

This study is an attempt to determine, by enucleation of one or both eyes, the influence of blinding on the visual centers of the brain both in the process of development and at maturity. Hybrid rats were operated on at three ages—on the day of birth and at the ages of 13 days and 4 months. The animals were killed when 7 months old. The degenerating nerve was filled with glia cells. In general, degeneration for seven months produced a higher glia cell content than that for three months. Shrinking of the optic tract and atrophy of the dorsal nucleus of the external geniculate body were proportionate to the duration of degeneration. Cells of the nucleus ventralis were not atrophied. The cells of the direct and those of the crossed projection field of the nucleus dorsalis presented a striking contrast. The second and third layers of the superior colliculus were atrophied by blinding in infancy, and the anteroposterior length was decidedly shortened. Peripheral blindness had no marked effect on the cells of the area striata seven months after operation. Tsang concludes that time is the decisive factor in inducing degeneration of the visual centers.

Fraser, Philadelphia.

BILATERAL INEQUALITY IN THE NUMBER OF SENSORY NEURONS IN THE TRUNK OF VERTEBRATES. ENZO DELORENZI, J. Comp. Neurol. **66**:301 (April) 1937.

Delorenzi had previously noted a difference of as high as 30 per cent in the number of sensory neurons in the second cervical ganglion of the right side and that of the left in the chick. He then undertook to find the differences for various segments of the trunk of new-born mice by determining the total number of neurons in all metameres. He observed great differences in the number of neurons on the two sides. Up to a certain point compensation for this difference was noted in the succeeding segments.

FRASER, Philadelphia.

INNERVATION OF THE INTRINSIC MUSCLES OF THE EYE OF THE CAT. SAM L. CLARK, J. Comp. Neurol. **66**:307 (April) 1937.

To study the innervation of the intrinsic muscles of the eye of the cat, Clark subjected a series of animals to one of the following operations: (1) removal of the superior cervical sympathetic ganglion on one side and part of the cervical portion of the trunk and of the remaining cervical ganglia; (2) section of the ophthalmic and maxillary divisions of the trigeminal nerve distal to the gasserian ganglion; (3) section of the oculomotor nerve intracranially; (4) removal of the ciliary ganglion, or (5) removal of the contents of the bulbus oculi. The cats were allowed to live for varying lengths of time. Nerve fibers from the cervical portion of the sympathetic chain enter the ciliary body, but supply only the blood vessels. No part of the ciliary muscle was observed to be denervated after cervical sympathectomy. Clark concludes that the ciliary muscle and the sphincter muscle of the pupil are supplied by the ciliary ganglion and that the dilator muscle of the pupil receives its fibers from the superior cervical ganglion.

ADDISON, Philadelphia.

FURTHER EXPERIMENTAL INVESTIGATIONS ON THE PHENOMENON OF HOMOLOGOUS RESPONSE IN TRANSPLANTED AMPHIBIAN LIMBS: II. NERVE REGENERATION AND THE INNERVATION OF TRANSPLANTED LIMBS. PAUL WEISS, J. Comp. Neurol. **66**:481 (April) 1937.

Weiss presents the anatomic details of nerve regeneration and innervation of transplanted limbs. These details were studied by gross anatomic dissection, electric stimulation and histologic preparations. The third, fourth and fifth spinal nerves contribute to formation of the forelimb plexus. The fifth nerve was usually used for innervation of the transplant. Transplantation of an additional limb in a swimming larva did not cause an increase in the number of cells within the corresponding spinal centers then connected with two limbs. The number of nerve fibers observed distally within each transplant equaled approximately that in a normal limb. The distribution of the nerves within a transplant duplicated with amazing accuracy the intrinsic pattern of a normal limb. The size of the regenerated branches in the transplant was close to normal. Tracing the nerves to their peripheral terminations by electric stimulation confirmed the nonspecific character of nerve regeneration. Removal of the old nerves from the proximal parts of the limbs prior to transplantation retarded nerve regeneration.

FRASER, Philadelphia.

FURTHER EXPERIMENTAL INVESTIGATIONS ON THE PHENOMENON OF HOMOLOGOUS RESPONSE IN TRANSPLANTED AMPHIBIAN LIMBS: III. HOMOLOGOUS RESPONSE IN THE ABSENCE OF SENSORY INNERVATION. PAUL WEISS, J. Comp. Neurol. **66**:537 (April) 1937.

In this study Weiss examined the function of transplanted legs in the axolotl in the absence of sensory innervation. Deafferentation was obtained by pulling out the dorsal ganglia and roots from the second to the fifth segment. Thirteen

animals survived. The first movements in the transplanted limbs appeared on the average at the end of twenty-eight days. The average time in experiments with mixed nerves was twenty-three days. Continued observation of the animals revealed that eventually a certain amount of sensibility reappeared in practically every limb. The evidence that homologous response appears in the same perfection with and without sensory control rests on six experiments. Histologic preparations of the spinal cord were made in order to confirm the absence of sensory connections in that area.

FRASER, Philadelphia.

FACTORS AFFECTING REGENERATION IN THE EARTHWORM. PRINCE SEARS CROWELL JR., J. Exper. Zoöl. **76**:1 (May) 1937.

Regeneration of heads and of tails in the earthworm Allolobophora caliginosa (Savigny) is related to the level along the main axis at which it occurs. Segments transplanted in an atypical position regenerate as they do in their normal position. The type of structure regenerating at a given level does not depend on the direction in which the regeneration occurs. The regeneration of a tail has no relation to the presence of a digestive tract. The region of the nerve cord concerned in regeneration does not determine the form of the regenerate, and regeneration of a head is possible in the absence of adult nerve cord of a head-forming region. Such a region, however, retains its capacity for regeneration of a certain type when transplanted to another region, even though it lacks its central nerve structures. The formation of lateral heads at the junction of two components may be induced by the cut ends of the nerve cord, but autogenous formation of a brain is possible if the nerve cord is absent. Nevertheless, in the regeneration both of heads and of tails, the nerve structures play an important part in the evocation of morphogenetic activity and may to some extent control the form of the regenerate.

WYMAN, Boston.

SUBSTITUTION OF LATERAL FOR AXIAL MESODERM IN RELATION TO THE DEVELOPMENT AND SEGMENTATION OF SPINAL GANGLIA. S. R. DETWILER, J. Exper. Zoöl. **76**:35 (May) 1937.

Further evidence that typical segmentation of spinal ganglia in Amblystoma larvae is subservient to a normal metameric arrangement of the adjacent axial mesoderm was obtained by removing the third, fourth, fifth and sixth somites (stages 26 to 28) and filling in the wound with a strip of lateral, unsegmented mesoderm with overlying ectoderm from a region just below from the seventh to the tenth somite. This mesoderm did not differentiate into muscle, but the space between the cord and the skin was occupied by loose connective tissue elements, and in several cases by a loop of the gut. Irregular segmentation of the ganglia in this region was evidence of lack of the influence of normally segmented mesoderm.

WYMAN, Boston.

Physiology and Biochemistry

THE OPTICAL PROPERTIES OF VERTEBRATE NERVE AXONS AS RELATED TO FIBER SIZE. FRANCIS O. SCHMITT and RICHARD S. BEAR, J. Cell. & Comp. Physiol. **9**:261 (Feb.) 1937.

Quantitative determinations were made of the inherent birefringence, and hence the ultrastructure, of the sheath elements of fibers of the frog's sciatic nerve, including axons with widely varying total diameters. These values, when plotted against fiber diameter, show no discontinuities from the smallest to the largest. In view of the shape of the curve, the differentiation commonly made between myelinated and nonmyelinated fibers is obviously arbitrary and not inherent in the ultrastructure itself. The change from proteotropic to myelotropic character occurs at a diameter of about 2 microns, which corresponds well with the size

arrived at by histologic methods as the dividing line between nonmyelinated and myelinated fibers. This change is due to the progressive and continuous increase in the relative amount of lipoid dispersed with the protein in the sheath as the size of the fiber increases.

CHORNYAK, Pittsburgh.

OPTICAL PROPERTIES OF THE AXON SHEATHS OF CRUSTACEAN NERVES. RICHARD S. BEAR and FRANCIS O. SCHMITT, J. Cell. & Comp. Physiol. **9**:275 (Feb.) 1937.

The metatropic reversal of birefringence is limited to a sheath surrounding the axis-cylinder (the metatropic sheath). The lipoids in the metatropic sheath are oriented in the living axon, the glycerin reversal serving to reveal this orientation by reduction of the form birefringence of the proteins in the sheath. Thus, the two factors which determine the optical properties of the myelin sheath of vertebrate nerves operate in a similar manner in the metatropic sheath of crustacean nerves. This thin sheath closely applied to invertebrate axons is comparable in ultrastructure to the myelinated sheath of vertebrate axons.

CHORNYAK, Pittsburgh.

POTENTIALS OF THE FIBER COMPONENTS OF THE COELIAC NERVE OF THE BULLFROG. GEORGE H. BISHOP, J. Cell. & Comp. Physiol. **9**:417 (April) 1937.

Lucas and Miksicek (1936) observed fibers arising from cells in the fourth spinal ganglion and coursing through the celiac nerve to the viscera, with no processes central to the ganglion which could be observed in sections stained either with osmic acid and silver, or pyridine and silver. No evidence of synapses in the dorsal root ganglion could be obtained. These fibers are of the small myelinated and nonmyelinated types and comprise the bulk of the fourth communicating ramus, which in turn forms from one half to two thirds of the celiac trunk. Bishop investigated these observations physiologically by recording action potentials. His results confirm the work of Lucas and Miksicek in demonstrating that when central processes of dorsal root ganglion cells cannot be demonstrated histologically electrical excitation is impossible. He is also unable to find evidence of any pathway by which these neurons can be activated normally in the body.

CHORNYAK, Pittsburgh.

ELECTRICAL STIMULATION OF POINTS IN THE FOREBRAIN AND MIDBRAIN: THE RESULTANT ALTERATIONS IN RESPIRATION. HERMAN KABAT, J. Comp. Neurol. **64**:187 (Aug.) 1936.

In order to provide accurate information on localization of function in the interior of the forebrain and midbrain, Kabat explored these regions in the cat by electric stimulation carried out with the Horsley-Clarke stereotaxic instrument. The respiratory responses are divided into four types: Type 1 is characterized by increase in the amplitude and usually in the rate of respiration; type 2, by acceleration of respiration with or without decrease in amplitude; type 3, by decrease in the rate or the amplitude of respiration or in both the rate and the amplitude, and type 4, by a significant increase in the amplitude of respiration with a corresponding decrease in the rate.

The type 3 response was most frequently elicited from the telencephalon. It was produced by stimulation of the septum pellucidum, preoptic area, anterior commissure, peduncular tract, rostral part of the gyrus genualis, genu of the corpus callosum and internal capsule. The type 2 response was obtained by stimulation of the ventromedial portion of the internal capsule. Few points in the telencephalon gave rise to a response of type 1. Stimulation of the stria terminalis near the crossing of the anterior commissure produced respiration of type 4.

Stimulation of the diencephalon usually elicited a marked increase in the amplitude and the rate of respiration (type 1). Stimulation of an uninterrupted column

extending the length of the hypothalamus gave the same response. This column has not been identified with any tract or nucleus. Other areas giving this response were the subfornical component of the medial bundle of the forebrain, the nucleus supra-opticus diffusus, the lateral hypothalamic area, the perifornical nucleus, the lateral mamillary nucleus, the region of the mamillary peduncle and the supramamillary commissure. The type 2 response resulted from stimulation of the internal capsule and other scattered areas. Type 3 respiration occurred during stimulation of the inferior thalamic peduncle, the habenula and the habenulopeduncular tract, the internal capsule and the nucleus reticularis thalami.

Stimulation of the mesencephalon, from the caudal end of the diencephalon to the lowest mesencephalic level explored, produced respiration of type 1. The type 2 response was obtained with stimulation of the central gray matter and the tegmentum. Respiration of type 3 was elicited from the habenula, the habenulopeduncular tract and the periventricular fibers. Although three types of respiratory response were elicited from the mesencephalic tegmentum, each type seemed to be localized in a distinct portion of this structure.

ADDISON, Philadelphia.

A PURRING CENTER IN THE CAT'S BRAIN. E. L. GIBBS and F. A. GIBBS, J. Comp. Neurol. **64**:209 (Aug.) 1936.

In the course of experiments with electric stimulation of the brains of 400 cats, 3 were found stimulation of which gave a purring response. The electrode was left in place; the animal was killed; the brain was removed and hardened in formaldehyde, and free-hand sections were made to determine the position of the tip of the needle. In each case it lay in the infundibular region. Thus, Gibbs and Gibbs conclude that purring can be elicited by electric stimulation in the infundibular region of the cat's brain. They do not associate this area with any nucleus or tract.

FRASER, Philadelphia.

FUNCTION AND STRUCTURE IN CHRONICALLY ISOLATED LUMBOSACRAL SPINAL CORD OF THE DOG. SARAH S. TOWER, J. Comp. Neurol. **67**:109 (June) 1937.

The lumbar and sacral dorsal roots of three 6 week old puppies were cut intradurally on both sides, and the spinal cord was transected above and below them, in an attempt to study the functional losses and residual activity in an isolated region of the spinal cord. The animals survived two, five and six months, respectively. Study of the living animal demonstrated that the isolated region of the cord had survived, together with its dependent peripheral nerves. Anatomic study of the isolated cord and the corresponding root ganglia and peripheral nerves showed many healthy cells and fibers and others with evidence of growth and repair. The cord caudal to the lower transection persisted as nerve tissue in only two animals. Tower concludes that these results accord with other evidence that nerve tissue is remarkably independent of functional stimulus for differentiation, growth and maintenance, that within the spinal cord and dependent peripheral nervous system trophic influence of one part on another derives from integrity of parts, without activity, and that autochthonous activity is not a property of the mammalian spinal cord.

ADDISON, Philadelphia.

THE EFFECT OF AVERTIN FLUID (TRIBROMETHANOL) ON THE BRAIN STEM: EXPERIMENTAL OBSERVATIONS. ROBERT R. WHITE, ROWLAND T. BELLOWS and WILLIAM P. VAN WAGENEN, J. Nerv. & Ment. Dis. **86**:1 (July) 1937.

Although it has been reasonably well established that avertin (tribromethanol) acts in part on the hypothalamus, clinical observations led White, Bellows and Van Wagenen to suspect that the drug acts also on the brain stem. Avertin may produce narcosis in cases in which the hypothalamic centers have been destroyed by tumor. The authors carried out experiments designed to demonstrate the effects of the drug on decerebrate animals. Decerebration was performed on dogs by

ligation of the basilar artery cephalad to the posterior or anterior cerebellar artery, followed at a second operation by ligation of the internal and external carotid arteries and their branches. After the onset of decerebration avertin was given intravenously in doses equivalent to 100 mg. per kilogram of body weight. White, Bellows and Van Wagenen record the results of the experiment on seven dogs. In five the injection of avertin produced flexion of some or all of the extremities for from twenty to seventy minutes. A second injection again produced flexion. In one dog decerebration was followed by extension and then by flexion; injection of avertin produced no change. In the seventh dog decerebrate extension was not affected by injection of the drug. In some cases righting reflexes were abolished by avertin. The authors conclude that avertin may have a pharmacologic action on the brain stem.

MACKAY, Chicago.

ASSOCIATED FACIAL, VOCAL AND RESPIRATORY COMPONENTS OF EMOTIONAL EXPRESSION. H. W. MAGOUN, D. ATLAS, E. H. INGERSOLL and S. W. RANSON, J. Neurol. & Psychopath. **17**:241 (Jan.) 1937.

Kinnier Wilson suggested that voluntary and emotional innervation of the facial muscles are effected by different systems within the brain, which explains the clinical picture of their dissociation. He postulated a mechanism in the brain stem which subserves the synkinesis of the facial, vocal and respiratory activities observed in emotional behavior. Magoun and his co-workers investigated these responses obtained from systematic electrical stimulation of the brain stem in lightly anesthetized cats and monkeys and in acute decerebrated cats. The stimulation was performed with the Horsley-Clarke instrument.

In the monkey faciovocal responses in the form of cries, barking noises and the like, accompanied by facial contractions, were obtained with each expiratory phase. There were two general forms of responses: (1) a combined excitatory and inhibitory type, consisting in initial apnea gradual appearance of the excitatory effects and their increasing development with continued stimulation, together with a post-stimulatory component and (2) a purely excitatory type, in which the vocal effects appeared with no latent period, continued at the same intensity and pitch throughout the stimulus and ceased at its conclusion. These responses were obtained from stimulation of a large part of the rostrocaudal extent of the central gray matter of the aqueduct, the dorsal part of the tegmentum of the midbrain, together with its lateral and ventral parts in the midbrain and pons, and the lateral part of the reticular formation of the upper medulla. The reactions of the first type were obtained only from the central gray matter and the adjacent dorsal portion of the tegmentum; those of the second type were obtained from all the stimulated regions. The accompanying changes in facial expression were regularly elicited by stimulation of the midbrain, rarely by stimulation of the pons and never by stimulation of the medulla. These differed from the results of direct stimulation of the facial nucleus and nerve in that they were usually observed in the contralateral half of the face; they synchronized with respiration and involved definite groups of facial muscles in producing the characteristic grimaces. The faciovocal responses were not obtained when the transition area from the thalamus to the midbrain was stimulated.

In the normal cat the vocal responses were, in general, cries or spitting reactions. The cries usually appeared without any latency and did not increase in intensity during the stimulation, nor were they accompanied by any facial expressions. The spitting reactions exhibited a minimum of vocalization and were associated with vigorous contraction of the facial muscles, usually in the half of the face opposite the site of stimulation. The localization of these responses in the normal cat was in foci situated in the rostral portion of the central gray matter surrounding the aqueduct, in the dorsal portion of the mesencephalic tegmentum and in the lateral, ventrolateral and ventral boundaries of the latter. The anterior portion of the hypothalamus was also found to be reactive in the normal cat, and

from this region spitting responses and cries, and at times purring, were elicited. These stimulated regions of the midbrain and pons in both the cat and the monkey did not correspond to the distribution of any well defined anatomic pathways.

In the decerebrate cat typical faciovocal responses were obtained which were identical with those elicited in normal cats. This suggested that the afferent connections to the thalamus or higher centers were not essential.

The authors conclude that the faciovocal reactions in the monkey and cat represent components of a fundamentally similar response, in consideration of the fact that various species of animals have certain characteristic modes of emotional expression. They resembled closely similar activity during the expression of unpleasant emotions by normal animals. The experiments indicate that the reactive area contains an efferent system for eliciting coordinated facial, vocal and respiratory activity during the expression of emotion.

N. MALAMUD, Ann Arbor, Mich.

ACTION POTENTIALS OF NORMAL MAMMALIAN MUSCLE: EFFECTS OF ACETYLCHOLINE AND ESERINE. G. L. BROWN, J. Physiol. **89**:220, 1937.

Records of action potentials obtained from the soleus muscle of cats indicate that the quick contraction elicited by the arterial injection of acetylcholine is a brief, asynchronous tetanus. From the analysis of records in which a number of units are in action, Brown concludes that the initial frequency is about 200 a second and that it gradually falls along a characteristic curve. The effect of physostigmine in producing a repetitive muscular response to a single maximal nerve volley was found to induce rates limited by the absolute refractory period. A second nerve volley is without effect if the interval between volleys is less than 20 milliseconds. Further separation produces gradual recovery from the effect of the second volley. In the presence of a dose of physostigmine insufficient to cause repetitive response to a single volley, the effects of two suitably timed volleys summate to give a repetitive response. The persistence in a weakly physostigminized muscle of acetylcholine in a concentration insufficient in itself to cause a response evokes a repetitive response to a single nerve volley.

McCOUCH, Philadelphia.

PHYSIOLOGIC PROOF OF SPINAL-PARASYMPATHETIC VASODILATOR FIBERS. K. KURÉ, S. SAITO and S. OKINAKA, Arch. f. d. ges. Physiol. **238**:290, 1936.

Stimulation of the fourth, fifth, sixth and seventh posterior lumbar roots and the first sacral root produces vasodilatation in the hindleg in dogs. This effect is prevented by the intravenous injection of a 1 per cent solution of nicotine, which, however, does not interfere with the vasodilator effect produced by stimulation of the sciatic nerve. Conduction in the centripetal fibers is not affected by the nicotine, since stimulation of the sciatic nerve and the posterior roots still elicits pain reactions. Kuré and his co-workers conclude that the vasodilatation is produced by stimulation of efferent autonomic fibers which synapse in the spinal ganglia. There is probably no second synapse in the periphery close to the endings of the vasodilator fibers since stimulation of the sciatic nerve still elicits vasodilatation after injection of nicotine.

SPIEGEL, Philadelphia.

Neuropathology

METASTASES OF INTRACRANIAL TUMORS. A. A. NELSON, Am. J. Cancer **28**:1, 1936.

A case of medulloblastoma of the cerebellum with discrete metastases to the vertebral bodies is described. The reported cases of metastasis of an intracranial tumor are reviewed. FROM THE AUTHOR'S SUMMARY. [ARCH. PATH.]

ACUTE HEMORRHAGIC ENCEPHALITIS ASSOCIATED WITH A MEDULLOBLASTOMA. CHARLES CRAMER, Arch. Path. **24**:52 (July) 1937.

Cramer reports a case of true hemorrhagic encephalitis in a man aged 23 with a tumor of the brain. The clinical picture was complicated by evidences of chronic encephalitis, the patient showing masklike facies, loss of associated movements in the upper limbs, slow and monotonous speech and rhythmic tremors of the lips and tongue. Coma, cyanosis and hyperpyrexia were terminal features. At autopsy two conditions were found: (1) multiple capillary hemorrhages, limited mainly to the subcortex, and (2) a medulloblastoma, involving the left basal ganglia. Histologically, the hemorrhages were observed to be mainly pericapillary and of the "ball hemorrhagic" rather than the "ring hemorrhagic" type.

WINKELMAN, Philadelphia.

DOUBLE ATHETOSIS WITHOUT STATUS MARMORATUS. J. M. NIELSEN and ELINOR R. IVES, Bull. Los Angeles Neurol. Soc. **2**:72 (June) 1937.

Nielsen and Ives discard the distinction between supposedly "primary double athetosis" unaccompanied by paralysis or spasticity, and "symptomatic bilateral athetosis," associated with varying degrees of spastic diplegia. They quote Vogt's description of double athetosis, which includes diplegia and contractures in many cases. Both Jakob and Josephy apparently considered status marmoratus as the invariable pathologic basis of double athetosis, but Wilson and others have pointed out that there is no constant pathologic condition which is responsible. Double athetosis should thus be considered as "the expression of disorder of a system," and not as the result of a specific anatomic lesion.

Nielsen and Ives report the case of a youth aged 19, whose birth had been difficult and who had had dysphagia since birth. In the early months of life his limbs began to move constantly. Later the lower extremities became rigid; contractures developed, and speech became dysarthric. Examination revealed constant athetotic movements of the entire body musculature, which were exaggerated by voluntary acts or emotion. Speech was dysarthric and almost unintelligible, and dysphagia was troublesome at times. Even mastication was made difficult by the constant involuntary movements. The lower extremities were somewhat spastic, and a questionable Babinski reaction was present on the left. There was also marked scoliosis. The patient died in collapse during administration of an enema.

Autopsy revealed an enormous megacolon. The cause of death was a thrombus in the conus arteriosus and pulmonary artery. The brain was grossly normal except for microgyria in the parietal regions. Microscopically, there were slight thickenings of the leptomeninges and diffuse oligodendrogliosis in the cortex. Deposits of brownish pigment were observed in some of the subpial cells. "There was no gross or microscopic evidence of status marmoratus or status dysmyelinisatus." The question of etiology in this case is thus unsettled. The authors think asphyxia is the main factor in producing double athetosis but believe that a faulty anlage cannot be excluded. In their opinion, athetosis may arise from disease of the cortex as well as of the basal ganglia.

MACKAY, Chicago.

POLIO-ENCEPHALOMYELITIS DUE TO BOTULISM. GABRIEL A. SCHWARZ, J. Nerv. & Ment. Dis. **86**:7 (July) 1937.

Schwarz states three concepts concerning the role of the toxin of Clostridium botulinum in botulism: (1) a specific action on the ganglion cells of the central nervous system; (2) a toxic effect on the vessels of the central nervous system, with changes in the ganglion cells secondary to alteration of the blood supply, and (3) a peripheral, curare-like action on the neural end-plate.

The earliest work in the field emphasized degenerative changes in the ganglion cells, such as vacuolation, chromatolysis and neuronophagia, which involved chiefly the motor cells of the nuclei of the brain stem and spinal cord, as well as the

cerebral cortex. There was soon observed, however, the frequent occurrence of vascular changes, which were regarded by some pathologists as primary. Conflicting observations and absence of lesions were frequently reported; eventually, in 1923, Pürckhauer's original (1877) theory of the peripheral action of the toxin was revived, and a curare-like effect on the motor end-plates of the cerebrospinal and parasympathetic systems was demonstrated experimentally. An attempt has been made to reconcile these various concepts with the theory that the botulinus toxin acts as a "general protoplasmic poison."

Schwarz reports the case of an Italian girl aged 16 who was admitted to the hospital with a history of diplopia, dysphagia, dysarthria, dizziness and weakness for three days. The symptoms began with nausea and epigastric discomfort and soon included also ptosis, photophobia and dimness of vision. Neurologic examination revealed bilateral involvement of the third, fourth, motor fifth, sixth, seventh, tenth and twelfth cranial nerves, with weakness of all extremities. Tendon reflexes were absent in the arms, and those in the legs were markedly reduced. The superficial reflexes were abolished. No sensory or trophic changes were found. The patient died on the fifth day after onset of the disease, of advancing bulbar, especially respiratory, paralysis. The leukocyte count was 14,000. Examination of the cerebrospinal fluid showed 4 lymphocytes per cubic millimeter, increase in globulin and 78 mg. of sugar per hundred cubic centimeters. Autopsy revealed gross edema of the brain, with cyanosis of the cortex on section. Hyperemia was noted in the midbrain, substantia nigra, reticular substance of the medulla, tegmentum of the pons and anterior horns of the cervical portion of the spinal cord. Hemorrhages were seen in the thoracic and lumbar regions of the spinal cord.

Microscopic examination revealed slight localized meningeal edema and infiltration. In the brain and spinal cord perivascular edema and slight infiltration with polymorphonuclear leukocytes, lymphocytes and macrophages were seen. In the cortex the small and medium pyramidal cells of lamina III were severely swollen and vacuolated. The large pyramidal cells in this lamina were better preserved but exhibited some perineuronal edema. The Betz cells were normal. There was likewise some vacuolation of the cells of the medial and anterior nuclei of the thalamus. The majority of the cells in the oculomotor nuclei were normal. A few contained small, irregular vacuoles, and others, eccentric and pyknotic nuclei with chromatolysis. The cells of the nuclei of the abducens, facial and motor part of the vagus nerves were markedly chromatolyzed. All the sensory nuclei of the brain stem were free from changes; in the cerebellum there were slight alterations in the Purkinje cells and some cloudy swelling of the cells of the dentate nucleus. In the spinal cord the most striking and important change was vacuolation, with lipoid deposits in the anterior horn cells at all levels, especially in the cervical and lumbar enlargements. The glial elements were largely free from change.

Schwarz believes that the diagnosis of botulism on clinical grounds is clear in his case. The pathologic observations correspond with those outlined in the original classic descriptions. In his case, however, the oculomotor nuclei were relatively unaltered, and there were no gross or microscopic thromboses and no changes in the vascular endothelium. Perivascular hemorrhages were infrequent and of minor importance. Furthermore, though the topographic distribution of the pathologic changes corresponded in general to the clinical features, it was not clear that the changes were altogether adequate to explain the clinical manifestations. The curare-like effect of the toxin may, in Schwarz' opinion, account for some of the symptoms.

MACKAY, Chicago.

HEME BODIES (ROSENTHAL FIBRES) ASSOCIATED WITH CAVITIES IN PONS AND CEREBELLUM AND ACOUSTIC NEURINOMA, WITH A REPORT OF TWO CASES. AMOUR F. LIBER, J. Neurol. & Psychopath. **17**:305 (April) 1937.

Rosenthal fibers are elongated microscopic bodies, which Liber prefers to designate as heme bodies because of their similarities to hemoglobin. Previously, they

have been observed near syringomyelic cavities, as a rule in connection with intramedullary tumor of the spinal cord and medulla. Liber describes for the first time a case in which Rosenthal fibers occurred in the pons and cerebellum, in association with an acoustic neurinoma. In both cases they were seen in the glial tissue surrounding cavities in the neighborhood of the acoustic tumor. This suggests that compression, cavitation and the presence of glial tissue are essential factors in their formation, although their exact etiology is still unknown.

N. MALAMUD, Ann Arbor, Mich.

CASES OF ACUTE CHOREA: REPORT OF AUTOPSY. C. I. URECHIA, Encéphale **31**:334, 1936.

Acute chorea is rarely fatal, and autopsies are rare. A previous anatomic study of a case was made by Urechia (*Rev. neurol.* **1**:522, 1928). The case here reported is that of a youth aged 17. Acute generalized chorea was present for seventeen days before death. There was slight fever. Cardiac signs and arthritis of the tarsus suggested a rheumatic etiology. Pericapillary hemorrhages and necrosis and chromatolysis were observed in the putamen, the caudate, amygdaloid and dentate nuclei and the corpus Luysi. In the putamen and caudate nucleus the small cells were chiefly involved.

LIBER, New York.

LESION OF THE LEFT INFERIOR FRONTAL GYRUS NOT ASSOCIATED WITH APHASIA. MARCOS VICTORIA, Encéphale **1**:85, 1937.

Victoria reports a case of a lesion of the left inferior frontal gyrus without associated aphasia in a woman aged 30, who was under observation for thirteen days before death. No disturbance of speech, except bradylalia, could be found, in spite of repeated neurologic examinations. There were slight paresis of the right side of the face, of central type; a bilateral pyramidal syndrome, more marked on the right, with clonus and a Babinski sign on the right; lateropulsions toward the right; bilateral papilledema, and tenderness on percussion of the left frontal bone. Later moria appeared. The patient was right handed. Necropsy revealed a syphilitic gumma, the size of "a cherry," in the ventral portion of the pars triangularis and pars opercularis of the left inferior frontal gyrus. The neighboring portions were less intensely infiltrated. At a distance were diffuse lesions of syphilitic meningo-encephalitis. Smaller gummas were also observed in other regions of the cerebrum. On the basis of his own case and of nine cases reported in the literature, Victoria agrees with Pierre Marie that motor aphasia cannot be attributed to a lesion limited to the pars opercularis of the left inferior frontal gyrus.

LIBER, New York.

INHERITANCE OF ECTOMESODERMAL BLASTOMATOSES WITH SPECIAL REFERENCE TO FAMILIAL TUMOR OF THE BRAIN. F. OEHLER, Arch. f. Psychiat. **105**:324 (Sept.) 1936.

Oehler reports a study of fifty-two cases of ectomesodermal blastomatosis of three types: Recklinghausen's disease, tuberous sclerosis and retinal and cerebellar angiomatosis. The Recklinghausen type is most frequently associated with familial occurrence either of similar tumors or of central acoustic neurinoma. Next in frequency is the so-called familial glioma, seven cases of which were reported as occurring in families. Next to these in frequency is familial tuberous sclerosis, and, finally, come the angiomatoses. Glioma is familial, cases usually occurring in the same generation. One cannot find among the cases of glioma reported instances in two or more generations, as in the other three types. In the last three forms it is probable that one is dealing with a dominant type of hereditary transmission.

W. MALAMUD, Iowa City.

SYMPTOMS AND HISTOPATHOLOGIC PICTURE OF GANGLIOCYTOMA OF THE MEDULLA OBLONGATA. ERHARD AMSTAD, Schweiz. Arch. f. Neurol. u. Psychiat. **39**:5, 1937.

Foerster and Gagel classified ganglion cell tumors as gangliocytomas, or tumors made up solely of ganglion cells, and ganglioneuromas, or tumors which in addition contain nerve fibers. The second group is subdivided into myelinated and amyelinated forms, depending on the presence or absence of myelin sheaths about the new-formed fibers. About fifty cases of ganglion cell tumor of the central nervous system have been reported. Amstad gives the clinical and postmortem observations in a case which he studied.

An underdeveloped youth aged 17 had been subject during childhood to nocturnal choking spells, attacks of dyspnea, nausea, pain in the upper part of the abdomen, difficulty in swallowing and vertigo. During the six months prior to admission to the clinic he lost weight and suffered from weakness, difficulty in swallowing and respiratory embarrassment. Two weeks before death fever, vomiting and persistent hiccup appeared. Extensive aspiration pneumonia, bilateral purulent otitis media and acute swelling of the spleen were observed at autopsy.

Study of the brain revealed internal hydrocephalus and a soft, infiltrating tumor extending from the first cervical segment to the lower limit of the pons, reaching its greatest extent in the right side of the medulla oblongata, at the level of the obex; it projected into the fourth ventricle. Histologically, the tumor was fairly vascular and had a stroma made up of glia cells. In some places septums of hyalinized connective tissue from the thickened pia extended into the tumor. Large vesicular nuclei with a definite nuclear membrane and a deeply staining nucleolus were seen in the tumor. Some cells had two nuclei, but direct evidence of either mitotic or amitotic division was lacking. The central portion of the cells was pale, as a rule, the Nissl granules being confined to the periphery. No definite endofibrils could be demonstrated. Myelin was not seen in the tumor, but otherwise the nerve fibers, which were not regarded as neoplastic, appeared to be intact.

Amstad believes that the tumor in his case developed in earliest childhood. He states that gangliocytoma of the medulla oblongata may produce symptoms at any time between the ages of 10 and 40, but most frequently between 15 and 20. The period elapsing between onset of symptoms and fatal termination varies from six months to ten years; it averages from three to five years. Bulbar involvement is indicated by respiratory and cardiac disturbances, as well as by difficulty in swallowing, vomiting and other gastric symptoms. The degree of involvement of the pyramidal tracts and sensory systems depends on the extent to which the cervical portion of the cord is invaded. Persistent hiccup is an important late symptom.

DANIELS, Denver.

CEREBRAL GLIOMATOSIS WITH DYSPLASTIC CHANGES IN THE CORD AND NEURINOMATOSIS OF A POSTERIOR ROOT. MAX BIELSCHOWSKY, Ztschr. f. d. ges. Neurol. u. Psychiat. **155**:313 (April) 1936.

Bielschowsky reports the case of a woman aged 40 who was admitted to the clinic because of weakness in the right arm and aphasia (mainly anomia) of nine weeks' duration. Neurologic examination showed weakness of the right lower part of the face and inability to protrude the tongue. The right corneal reflex was absent. The small muscles of the right hand were atrophic. Later in the course of the disease, weakness in the right leg appeared. The Babinski and Oppenheim reflexes were elicited bilaterally. An epileptic attack, with movements beginning on the right side, was observed on the second day of hospitalization. The patient died fourteen days after admission.

Autopsy disclosed a spongioblastoma multiforme, the size of a hen's egg, in the periventricular region of the left parieto-occipital lobe. At the level of from the eighth cervical to the first dorsal segment of the cord a mass of glial tissue, not invasive or infiltrating in character, replaced some of the anterior horn cells. The lesion was in the median position and was composed of small glia cells and

astrocytes. All along the cord, especially dorsal to the ventral commissure and extending into the ventral part of the posterior horn, similar collections of glial tissue were observed. Demyelination was present, especially in the ventral part of the posterior columns. Double and triple central canals were observed, all of which were well formed and lined with intact ependyma. A small neurinoma was seen in one of the posterior roots of the third lumbar nerve. Bielschowsky believes that all the changes described are due to defective development. The periventricular site of the intracerebral glioma argues for its origin from embryonic cells in that region.

SAVITSKY, New York.

CROSSED THALAMOCEREBELLAR ATROPHY. V. W. D. SCHENK, Psychiat. en neurol. bl. **41**:218, 1937.

Schenk describes the brain of a man aged 61 who became epileptic and mentally abnormal after a fall, at 2 years of age. The only neurologic sign was a questionable Babinski reflex on the right. Histologically, the left inferior olive was atrophied, orally and dorsally. The olivocerebellar fibers in the restiform body were absent, and the cortex of the right cerebellar hemisphere, except the flocculus, was atrophic. The right dentate nucleus, the right brachium conjunctivum and the left red nucleus, as well as the left rubrothalamic tract, were smaller than the corresponding structures of the opposite side. The most severe atrophy was observed in the left anterior thalamic nucleus, the cells and fibers of which had completely disappeared. There was less atrophy in the lateral thalamic nucleus. The left medial nucleus of the mamillary body and the bundle of Vicq d'Azyr were also atrophic. Atrophy of from 20 to 30 per cent occurred in cortical areas $6a\alpha$ and $6a\beta$ and of from 10 to 20 per cent in areas 8, 9, 11, 25 and 33. Schenk assumes that the primary lesions was agenesis of immature, growing elements in the optic thalamus. The degenerations in the mamillary body and in the rubrocerebellar system caudal to the inferior olive were considered of retrograde nature. The mild degree of atrophy in the internal capsule was probably dependent on degeneration of the frontothalamic and the thalamofrontal fibers. In contrast to the usual cases of crossed cerebrocerebellar atrophy, crossed thalamocerebellar atrophy apparently is rare.

LEWY, Philadelphia.

Psychiatry and Psychopathology

SOMATIC PHENOMENA IN PSYCHONEUROSES. JOHN M. FLYNN, Am. J. M. Sc. **193**:548 (April) 1937.

Flynn studied a group of eleven women and nine men, whose average age was 29 years. Fatigue, digestive complaints and excessive perspiration were presenting symptoms in 90 per cent. All the patients had low blood pressure, and 90 per cent had definitely increased sugar tolerance. With physical therapy the symptoms disappeared, and the physical abnormalities were replaced by normal findings in eight cases. Flynn believes that all twenty patients showed a common psychic pattern in that all were faced with situations which were disliked and intolerable and which could not be altered. With thorough mental catharsis there were disappearance of symptoms and restoration of the patients to health, both mental and physical. It is inferred that the patients had symptoms and signs by reason of hyperactivity of the parasympathetic system or hypo-activity of the sympathetic system. It is suggested that psychic factors can produce a predominantly parasympathetic orientation of the autonomic system.

MICHAELS, Boston.

FEARS OF ONE THOUSAND COLLEGE WOMEN. MARIE HACKL MEANS, J. Abnorm. & Social Psychol. **31**:291 (Oct.-Dec.) 1936.

In an effort to determine what Alabama College girls fear and the extent of the fear, a schedule of various possible fear stimuli was arranged from a list collected

from 1,000 women at Alabama College during the year 1929. Of the 490 fear stimuli presented, a revised list of 349 items was submitted for scoring to 1,000 women at the college during the year 1930. The percentage of times each fear stimulus was marked by the 1,000 women was then computed, as well as the average intensity of the stimulus, rated on the basis of from 1 to 5 (5 indicating maximum intensity). The percentage of frequency was multiplied by the average intensity to arrive at a relative value for each of the 349 possible stimuli. For instance, fear of "chickens" was marked by 6 per cent of the women, with an average intensity of 1.78. Therefore the relative value assigned to it was 10.7. To eliminate working with fractions, each relative value was multiplied by 10. The 10.7 value for "chickens" then would be expressed as 107. The fear stimuli were then tabulated in columnar form according to their relative values, the objects most often and most intensely feared being nearer the top. Heading the list of all possible objects of fear was "snakes."

A study of the table reveals something of the psychologic reactions of the college woman. She is afraid of snakes, bulls, mad dogs and spiders, but not particularly of mice. She is not, as is often claimed, indifferent to the fate of loved ones. She fears insane persons and drunken men more than insanity or being intoxicated. She is more fearful of murderers than of being murdered, of guns than of being shot and of hypodermic needles than of pain. Evidently the instrument is more feared than the act performed with the instrument. She is equally afraid of leprosy and of venereal diseases, but is more afraid of tuberculosis than of heart failure. She is not afraid of spinsterhood, and even less of marriage, but she fears being disappointed in love. Being penniless or dependent was not terrifying to her in 1930, whatever her reaction may be today. She is much more afraid of choosing wrong friends than of being lonely. She is fearful of being criticized and of being ridiculed, but not of being unconventional.

In the directions for scoring, the students were requested to indicate each fear stimulus of known origin and to state on the back of the schedule the origin of the stimulus and the age at which it occurred. Only 383 of the 1,000 students had any knowledge of the origin of their fears. In only 614 of the 1,101 instances in which the fear had a known origin was the age designated. In 99 cases the origin was stated to have been between the ages of 1 and 6 years; in 279, between 7 and 12; in 201, between 13 and 18, and in 35, between 19 and 24. Reexamination at varying intervals during the four years of college life revealed that little shifting of the types of fears had occurred.

WISE, Howard, R. I.

DELINQUENCY AMONG JEWS. LIEBMANN HERSH, J. Crim. Law & Criminol. **27**:515 (Nov.-Dec.) 1936.

Hersh analyzed the criminal statistics of Poland, in order to compare the ratio of criminality for the Jewish with that for the non-Jewish population. He found that the general ratio of criminality for Jews is one-half that for non-Jews both in ex-Russian and in ex-Austrian Poland. However, in offenses against the state and social order the Jews show a ratio of about 118 per cent, as against that for non-Jews. For Jews the ratio of criminality against persons is about 45 per cent of that for non-Jews, and against property, it is about 30 per cent. Trading in stolen goods is a frequent crime among Jews. Simple theft is from three to four times less frequent among Jews than among non-Jews. Brigandage is rare among Jews, and sacrilegious theft is practically nonexistent. In all other categories of theft Jews commit only one-fourth as many offenses as non-Jews.

SELLING, Detroit.

DO PROBLEM CHILDREN BECOME DELINQUENTS AND CRIMINALS? NATHAN BODIN, J. Crim. Law & Criminol. **27**:545 (Nov.-Dec.) 1936.

Bodin reports a survey of 116 adult persons who had been considered, from ten to fifteen years previously, to be problem children in the schools of Berkeley,

Calif. They were originally studied chiefly at the ages of from 13 to 14, although in some cases the conduct disorders presented themselves as early as at 8 years of age. The average age of these persons during the present survey was from 22 to 23. The original mean intelligence quotient was 79. The girls had been arrested chiefly for sexual misconduct and the boys for varied offenses. Of the arrests 31.3 per cent were for larceny and offenses against property, and most of the others were for "incorrigibility." Fifty-four and five-tenths per cent of the offenders had been arrested more than twice, and 26.6 per cent more than five times. Ninety-two and five-tenths per cent have since become delinquents and criminals, and 50.6 per cent had first become delinquent in the preadolescent period. It is concluded that while the apparent result of referral to the Bureau of Research and Guidance is not good, the bureau in reality has not failed, for the following reasons: (1) It was not until eight years ago that modern methods of treatment were installed; (2) there was a large percentage of subnormal and feebleminded children in the group, and (3) the work of the bureau has been curtailed. Bodin suggests further research for determination of the factors involved in the problem.

SELLING, Detroit.

FOLLOW-UP STUDY OF 100 PATIENTS DIAGNOSED AS "NEUROSIS." BERNARD COMROE, J. Nerv. & Ment. Dis. **83**:679 (June) 1936.

Comroe made a follow-up study of 250 patients' conditions diagnosed as neurosis. Replies which should be regarded as having definite value were available in 100, or 40 per cent of the cases. In 24 of these 100 cases definite evidence of organic disease became manifest after discharge of the patient, with a time interval averaging eight months, but never of more than two years. In 7 of the patients death was attributed to abdominal carcinomatosis, carcinoma of the liver, gastric carcinoma, disease of the coronary arteries, Addison's disease, pellagra, or myocardial degeneration.

The author remarks that many physicians consider the diagnosis of neurosis one of exclusion, whereas the condition is really an emotional instability out of proportion to the organic impairment of the patient. Failure to obtain a complete history is in many instances the outstanding error. Comroe stresses the importance of investigating the psychic problems of the patient as much as the medical history. Organic disease and neurosis may coexist, and either may prove the forerunner of the other. If a diagnosis of neurosis is made, careful periodic check-ups should be made to exclude the presence of organic disease.

HART, New York.

SOME MATE SELECTION STANDARDS OF COLLEGE STUDENTS AND THEIR PARENTS. RAY ERWIN BABER, J. Social Hyg. **22**:115 (March) 1936.

In Baber's course entitled "Marriage and Family Life" the students were asked to designate, according to an outline, their attitudes on the selection of a mate. The study covers a period of six years and represents the replies of 642 boys and girls. Baber points out that the replies may be considered as a fairly typical sample of attitudes of the student body of New York University but may not represent those of young people the country over. Also, the study is frankly subjective and hence subject to the limitations of that method.

Economic status was of small concern. More than nine tenths of the boys and four fifths of the girls said that they would marry a person with a smaller purse than their own. Two thirds of the boys said that their mates should not be too far down in the scale of beauty, while one third were willing to discount this factor, if all others were satisfactory. Four fifths of the girls were willing to waive the question of good looks. Both the boys and the girls were in accord that disposition and personality were the most important element of a happy relationship. On the question of morals, 80 per cent of the women insisted that the standards of their mates should be as high as their own; only 71 per cent of the men made a similar

demand. Three fourths of the women and nearly four fifths of the men were willing to marry into an inferior family. About two thirds of the girls and three fifths of the boys were willing to disregard differences in religious faith, but very few would adopt the religion of the spouse. Only 1 girl in 24 and 1 boy in 16 were willing to assume the handicap of a mate in poor health to begin with; half of them were willing to marry the prospective mate even in poor health if the ailment developed after a close friendship had been formed. Less than a fifth of the girls were willing to marry a man of a lower intellectual or educational level than their own. Three fourths of the men were willing to marry a girl who was not their equal in these respects. Almost all the girls wanted their partner to be older than themselves—five years older being the median and ideal choice. Only 75 per cent of the men wanted a wife younger than themselves; 24 per cent wished her to be of the same age, and 1 per cent preferred her to be older.

A comparison of the students' attitudes with those of 200 parents reveals interesting differences. The parents were willing, by a large majority, for their sons, and even their daughters, to marry a person of lower economic rank, but not as willing as the young people themselves. The sons insisted much more on beauty in their mates than did the parents. Daughters and parents were about equally agreed that good looks were not essential. The parents placed only a little more stress than the young people on disposition and personality. Great differences existed regarding moral standards, inferiority of family and religion; the parents stressed the importance of these factors much more than the students. Regarding health, parents and students were agreed on the question of marrying a person in poor health at the beginning but not on that of marrying one whose poor health had developed after a close friendship had been formed. The sons were more willing to marry a girl of lower intelligence than the parents were to permit them, but both fathers and mothers were more willing for the daughters to marry men below them intellectually or educationally than were the daughters themselves. On the age factor parents and children were in substantial accord.

When the students were asked to vote for five characteristics in the order of their importance, the men named disposition and personality, health, intelligence and education, beauty and moral standards. With the women "the same religious faith" and moral standards tied for the fourth and the fifth place respectively. The girls insisted less on good looks than on anything else. The parents rated health first and then intelligence and education, disposition and personality, the same religious faith and moral standards; they rated lowest beauty or good looks.

FERGUSON, Niagara Falls, N. Y.

ASSOCIATION-MOTOR INVESTIGATION IN CLINICAL PSYCHIATRY. FRANKLIN G. EBAUGH, J. Ment. Sc. **82**:731 (Nov.) 1936.

The material presented in this paper is based on the association-motor records of 100 normal subjects used as controls and 297 psychiatric patients studied during the past three and one-half years. The procedure follows essentially the principles introduced by Luria and subsequently modified by Ebaugh to meet the requirements of every day clinical practice. The patient is requested to make responses to a list of words, following Jung's word association technic. At the same time, the motor responses are recorded by means of mechanical receptors on which the patient's hands rest. This technic has been found of great value in psychotherapy. The patient often has difficulty in accepting an emotional cause for his illness. The words which have especial emotional importance for him, the so-called complex indicators, show a prominent motor response and he can be shown these responses on the motor curve in order to prove that certain topics are of especial significance to him. The disorganization is much less evident after successful therapy, and if this is demonstrated to the patient a certain amount of reassurance and confidence is gained.

KASANIN, Chicago.

CHRONAXIMETRIC STUDIES IN CATATONIA. S. L. LAST and ROLF STROM-OLSEN, J. Ment. Sc. **82**:763 (Nov.) 1936.

Measurements of chronaxia were made on the muscles of the upper and lower limbs in cases of severe catatonia. Abnormal figures with marked variability were found in all cases. The authors are at a loss to explain the great variability in the chronaxia of muscles of catatonic patients.

KASANIN, Chicago.

THE DIFFERENTIATION OF NEUROSES AND MANIC-DEPRESSIVE PSYCHOSES. DESMOND CURRAN, J. Ment. Sc. **83**:156 (March) 1937.

There is much confusion in psychiatric literature concerning the differentiation of manic-depressive psychoses and neuroses. True differentiation is often difficult, if not impossible. In general it is held that in a psychosis endogenous constitutional factors play a predominant part, the psychologic factors being secondary. The patients recover in time, for endogenous reasons. Such patients are not suitable for psychotherapy, which may even be harmful. On the other hand, in the neuroses, psychologic factors are predominant. Such patients must be treated with active psychotherapy, since they do not "drift" into good health. The author presents his criteria for differentiation of the two conditions.

Psychoses	Neuroses
1. Subjective complaint of depression.	1. Subjective complaint of "anxiety" or "fatigue."
2. Somatic complaints absent or not important.	2. Somatic complaints prominent.
3. Remorse and self-reproach present.	3. Remorse and self-reproach absent or "insincere."
4. Patient does not blame others.	4. Patient blames others.
5. Loss of weight invariable.	5. Loss of weight not invariable.
6. Constipation invariable.	6. Constipation not invariable.
7. Depersonalization present.	7. No depersonalization.
8. "Adequate" precipitating factor often absent; cause often not discoverable.	8. "Adequate" precipitating factor often present; cause discoverable or clear.
9. Steady course strikingly independent of environment.	9. Unsteady, variable course, dependent on environmental factors.
10. Patient healthy except for circumscribed attacks.	10. Patient seldom absolutely well.
11. Positive family history.	11. Negative family history.

Curran believes that it is necessary both to modify and to enlarge the conception of what constitutes a manic-depressive type of reaction. It is also necessary to admit that there are cases in which a mixture of both manic-depressive and neurotic features is shown. This does not mean that all attempts at clinical grouping should be discarded. Curran believes that the manic-depressive psychosis is as accessible to therapy as the neurosis. He maintains further that attempts to establish artificial dichotomies between neurosis and manic-depressive psychosis is harmful since it does not settle either problem.

KASANIN, Chicago.

A CASE OF HYSTERIA SHOWING SPONTANEOUS HYPERVENTILATION TETANY. RUSSEL FRASER, J. Ment. Sc. **83**:190 (March) 1937.

Fraser describes a case of hysterical epilepsy, with genuine seizures induced by hyperpnea. The patient, a probation nurse, had had seizures in childhood during an attack of whooping cough. The recent symptoms began three months before hospitalization, during her hospital training, in which she found it difficult to deal with many problems concerned with her personal relations and work. After her admission to a hospital for mental disease, it was observed that the attacks followed extremely rapid respirations of from 70 to 80 per minute. Seizures occurred also

when the patient was asked to hyperventilate at the rate of from 40 to 50 per minute. Extreme hyperpnea preceded the seizures; it was a prominent feature in all stages, with unconsciousness at the height of the seizure. During the seizures the eyes turned upward; small twitches were visible in the face; the tendon reflexes were exaggerated, and the Chvostek sign was elicited. Studies of the blood during the convulsive seizures showed definite alkalosis, and the seizures could be terminated either by correcting this or by giving calcium intravenously.

Fraser points out that spontaneous tetany following hyperventilation is most frequent in association with hysteria but that loss of consciousness is rare. He points out also that epilepsy of hysterical origin usually disappears after adjustment of the patient to his personal problems.

KASANIN, Chicago.

LONELINESS AND THE PARANOID SYNDROME. D. N. PARFITT, J. Neurol. & Psychopath. **17**:318 (April) 1937.

Paranoid reactions commonly occur in women during the involutional and senile periods. Some etiologic factors which have been stressed are the cerebral changes and the psychologic difficulties characteristic of involution and senility. Parfitt draws attention to the frequency and importance of the factor of loneliness in the development of the psychosis and illustrates this with reports of six cases. He emphasizes the introversion as well as the social isolation which is characteristic of this age period. The sexual and persecutory delusions are expressions of both the projection of guilt and the acquisition of attention. Early efforts to overcome the factor of loneliness influence the prognosis favorably.

N. MALAMUD, Ann Arbor, Mich.

IMAGE OF THE CORPOREAL SELF AND ITS PATHOLOGIC DEFORMATIONS. JEAN LHERMITTE and E. TCHEHRAZI, Encéphale **1**:1, 1937.

The semeiologic value of the corporeal image of the self was first noted by Pick, who designated as autotopognosia the inability to carry out "reflected movements," i. e., to touch a given point of one's body at will. Analysis of this disorder shows that for a subject with intact senses visual information is most important, while exteroceptive as well as proprioceptive stimuli play a minor role. Thus, in a case reported by Lhermitte and Trelles the patient could touch a point on his body only while looking at a mirror. The image of the bodily self results from a combination of physiologic and psychologic mechanisms, as Charcot showed in cases of fantom limbs, and cannot be localized anatomically in the central nervous system. Autoscopy must be viewed with prudence, as in many instances it is probably mystification. Yet cases occur in which it is associated with organic nervous disease. Likewise, in dreams the dreamer often sees his double. Thus, a physician with angina pectoris saw in a dream his double suddenly grow pale, experience intense pain in the chest and stop short as he was climbing a tower. Deformations of the self-image have been observed in cases of total transection of the thoracic cord, with anatomic control, in which the patients experienced peculiar, often definitely localized, sensations in the anesthetized and paralyzed lower extremities. In a case of left hemiplegia the left arm was believed to belong to the patient's neighbor. In a case of right hemiplegia the paralyzed arm seemed discontinuous, as if there were "a hole" between the upper part of the arm and the hand. Autotopognosia was observed in apraxic patients by Lhermitte and Trelles. A peculiar type of autotopognosia is seen in digital agnosia. The patient cannot name, distinguish or move a given finger on command, yet he can use his fingers correctly in automatic gestures. Dissolution of the self-image, either partial or complete, plays an important part in apraxia. There are probably no pure apraxias, only apractagnosias. The self-image is often altered in various intoxications, especially in that produced by peyotl. Thus, one subject perceived the soft parts of his head become as thin as paper, while he saw himself as if he were in a chinese lantern, looking at the room through a papyraceous cheek.

LIBER, New York.

Diseases of the Brain

FUNCTIONAL HYPOGLYCEMIA OF CHILDHOOD, WITH PARTICULAR REFERENCE TO RECURRENT CONVULSIVE MANIFESTATIONS. JOHN MOTT RECTOR and R. E. JENNINGS, Am. J. Dis. Child. **53**:1012 (April) 1937.

The cases of eleven children with convulsions associated with hypoglycemia are reported. The symptoms began in most instances between the ages of 1 and 3 years. Most of the attacks occur late at night, early in the morning or several hours after meals. The hypoglycemia is usually intermittent and recurrent and associated functionally with a lowered glycogen reserve as a result of anorexia, vomiting, pyrexia, excitement or excessive muscular effort. A progressive course unaccompanied by improvement with diet justifies the consideration of exploration for a neoplasm of the pancreas. The diagnosis rests on a convulsive or postconvulsive level of the blood sugar of less than 70 mg. per hundred cubic centimeters associated with a therapeutic response to dextrose. The treatment during convulsions consists in intravenous injections of dextrose. Hypnotics are of no apparent value. Prophylactic therapy consists in a diet moderately high in carbohydrate, with feedings between meals. If this is not efficacious, a mildly ketogenic diet is desirable.

WAGGONER, Ann Arbor, Mich.

TORULA INFECTION OF THE CENTRAL NERVOUS SYSTEM. EDWARD A. LEVIN, Arch. Int. Med. **59**:667 (April) 1937.

Although only sixty cases of this condition have been reported in the literature, it is probable that torular infestation of the nervous system is less rare than this figure suggests. It has probably often been diagnosed erroneously as cerebrospinal syphilis, tumor of the brain, meningitis or encephalitis. The organism is widely distributed in nature, presumably enters the body through the upper respiratory tract and has a special predilection for nerve tissue. It grows readily on acid mediums, but so slowly that it may be missed if the culture tubes are discarded within four or five days. The disease can be transmitted to animals, and for diagnostic purposes the suspected organism, suspended in saline solution, should be injected intraperitoneally into white mice. The animal succumbs to the infection within a month; at autopsy the torula can be cultured from the brain, lung and kidney.

Clinically, the disease manifests itself by headache, nausea, stiffness of the neck, vertigo and mental symptoms, which may be of sudden, but usually are of gradual, onset. Choked disks are frequent. As the condition progresses loss of weight occurs; the patient becomes comatose and dies. The disease occurs most frequently in men but shows no racial or geographic preferences. Examination of the blood is ordinarily not illuminating in cases of torulosis, but study of the spinal fluid is important. The fluid may be clear, turbid or yellowish. Cells, albumin and globulin are increased, and a colloidal gold curve suggestive of meningitis or syphilis is usual. The sediment secured from a centrifugated specimen of spinal fluid may reveal the yeastlike cells, and a smear of this will often show the typical organism. Culture and animal inoculation are essential for absolute diagnosis.

Levin describes two cases, in one of which the original diagnosis was meningitis and in the other syphilis. Both patients were men in late middle life. The first patient had had headache, vomiting, weakness and blurred vision for five years. He was apathetic; neurologic examination gave evidence of chronic choked disk and indicated a space-taking cerebral lesion, which was shown at autopsy to be torular infestation. The spinal fluid of this patient was xanthochromic; the cell count varied in different specimens from 75 to 280; the sugar was decreased, and the mastic curve showed an elevation in the middle zone. The second patient had had headache, vomiting and dizziness for several months. Papilledema was present. The spinal fluid pressure was 300 mm., and the cell count was 160, with

most of the cells lymphocytes. In both cases examination and culture of the sediment from the spinal fluid, combined with animal inoculation, established the diagnosis during life. No treatment is known, and on reviewing the literature, Levin finds that in all proved cases the outcome was fatal.

DAVIDSON, Newark, N. J.

NEURO-OTOLOGIC STUDIES IN EPILEPSY. EDWIN J. BLONDER, Arch. Otolaryng. **25**:63 (Jan.) 1937.

Forty-three patients with idiopathic and twenty with organic epilepsy were given careful neuro-otologic tests to discover whether anything characteristic of epilepsy could be noted. The hearing, caloric and galvanic tests were studied carefully. The authors conclude that there were no findings characteristic of any group of these patients.

HUNTER, Philadelphia.

THE FRIEDMAN TEST AND PITUITARY TUMOR. E. P. MCCULLAGH and W. K. CUYLER, Endocrinology **21**:8 (Jan.) 1937.

McCullagh and Cuyler performed the Friedman test in a selected group of 946 nonpregnant persons and observed 209 positive reactions. Endocrine disease was suspected in each case. In 131 cases in the group a clinical diagnosis of pituitary disease was made, and excessive amounts of gonadotropic substance were found in the urine by means of the test in 59 of the cases. Of the cases in which the diagnosis of pituitary disease had been made, pituitary tumor was present in 15. Of the 8 cases of pituitary neoplasm in which a positive Friedman reaction was found, the diagnosis was verified in 4—at necropsy in 3 and at operation in 1. In 2 cases the clinical evidence of tumor was clear. In 2 cases in which the evidence indicating the presence of pituitary tumor was less striking, there were outspoken clinical acromegaly and enlargement of the sella turcica, although there was no distinct bony erosion of the sellar boundaries and no changes in the visual field. Of the 7 cases of pituitary tumor in which a negative Friedman reaction was obtained the diagnosis of tumor was verified in 4 — at necropsy in 1 and at operation in 3. In the first 2 cases there was a questionable excess of gonadotropic substance, but since the reactions were not positive, these are included in the group. In the remaining cases the Friedman tests gave completely negative results. In cases of pituitary tumor in which the Friedman reaction is positive, roentgen therapy to the pituitary may be followed by marked diminution in the excretion of gonadotropic substance as judged by the test; in 2 instances this was accompanied by diminution in the excretion of androgen.

EDITOR'S ABSTRACT.

HEREDITARY FACTORS IN EPILEPSY: DIFFERENCES BETWEEN DETERIORATED AND NONDETERIORATED PATIENTS. H. A. PASKIND and M. BROWN, J. A. M. A. **108**:1599 (May 8) 1937.

Paskind and Brown describe the hereditary factors in a group of well adjusted, nonpsychotic, nonfeebleminded extramural persons with epilepsy and determine whether these patients have a different heritage than institutional, deteriorated patients. Of the 31 patients studied, 139, or 42 per cent, had a family history of no significance. In the remainder, or 58 per cent, there were evidences of a hereditary neuropathic taint. The authors state that their data regarding heredity are best compared with those of Snell. Of 345 cases he found evidences of a familial neuropathic trend in 81.26 per cent, a ratio of 23.2 per cent higher than that in their series. From this it is reasonable to believe that hereditary neuropathic taint is more frequent in deteriorated, institutional patients. In the authors' series a neuropathic factor could be detected in the direct line (parents) in 41 per cent, in the indirect line (grandparents, uncles and aunts) in 10.4 per cent and in siblings in only 6.6 per cent. These data as compared with those for institutional patients indicate that the nondeteriorated patients showed a smaller percentage of

hereditary taint in the direct and indirect lines. In the siblings of nondeteriorated patients, tainting was more frequent (from 6.6 to 5.4 per cent). Migraine and nervousness were more common in parents of the nondeteriorated patients, but psychosis was more than five times as frequent in the institutional as in the extramural patients, epilepsy more than three times as frequent, alcoholism more than eight times as frequent and apoplexy more than twice as frequent. In their series 0.6 per cent of the parents had psychopathic personality; in Snell's series of institutional patients this ratio was 10.79 per cent. It thus appears that the parents of the deteriorated, institutional patients with more malignant epilepsy are much more heavily burdened with neuropathy than are the parents of the nonpsychotic, extramural epileptic persons. The 331 nondeteriorated patients had 375 relatives showing evidences of a neuropathic taint. Epilepsy was found in the family in 8.4 per cent, mental disease in 3.5 per cent and alcoholism in 4.3 per cent. Figures for these values as given in the literature far exceed those obtained in the present study, with two exceptions: Starr found that in his patients there was a history of epilepsy in the family in 7 per cent, but his series was drawn from private practice and outpatient clinics. Turner found alcoholism in 3.1 per cent of his patients. This affords further evidence of the difference in heredity between patients institutionalized because of mental changes and those who are well adjusted outside an institution.

EDITOR'S ABSTRACT.

MUSICOGENIC EPILEPSY. M. CRITCHLEY, Brain **60**:13 (March) 1937.

Critchley describes the occurrence of epileptiform attacks in factual association with the hearing of music. He cites four personally observed cases and seven cases seen by colleagues. Cases of this phenomenon are too rare to permit dogmatic conclusions as to the clinical features which may be regarded as characteristic. From such evidence as is available, however, it appears that the association between stimulus and attack is close; only rarely does a seizure occur without the precipitating factor of music. On the other hand, music may be heard without an epileptic attack necessarily following. There is reason to believe that in some cases only certain types of music may be followed by unconsciousness. An attack does not usually follow promptly the onset of the music, and the stimulus may need to be maintained for many minutes before producing a fit. The character of the epileptic phenomena proper varies from transient "absences" or obfuscations of consciousness to complete major attacks, with convulsive movements and vesical incontinence.

EDITOR'S ABSTRACT.

CEREBRAL CONGESTION AS AN AETIOLOGICAL FACTOR IN EPILEPSY. RONALD M. CAIRNS, Brit. M. J. **1**:388 (Feb. 20) 1937.

Cerebral congestion resulting from a large carcinoma in the mediastinum is given as the probable cause of generalized epileptic seizures in a man aged 49. Papilledema, cyanosis and swelling of the face and congestion of the veins of the neck and arms were among the other findings. Necropsy, performed six weeks after onset of the illness, showed no other possible cause for the convulsions.

ECHOLS, New Orleans.

PYKNOLEPSY. H. L. PARKER, Irish J. M. Sc., February 1937, p. 70.

Parker states that pyknolepsy is rare. Certain features of pyknolepsy tend to separate it from the more common clinical syndrome of petit mal. Girls are more commonly affected than boys, and the family history is usually free from epilepsy, mental disease and kindred diseases. The onset is between the ages of 4 and 10 years, and, while in the case reported the progress of the disease was gradual, usually it is abrupt and overwhelming from the beginning. There is a stereotyped character of the attack, as in petit mal, which rarely changes throughout the course

of the disease. The characteristic feature, however, is its extreme brevity, so that the duration of the attack is a few seconds and is considerably shorter than that of the average petit mal seizure. Another distinguishing feature is the extreme frequency with which the attacks occur. They may reach the striking total of a hundred a day. The degree of loss of consciousness is slight and is perhaps the principal feature. The patient never falls and may continue to carry out in a more or less efficient manner activities in which he was originally engaged. While petit mal shows little response to antiepileptic drugs, such as bromides and phenobarbital, pyknolepsy does not respond at all. There are certain reasons that it is important to recognize pyknolepsy, even though its existence as a clinical entity may be doubted. Several months or years may be necessary for this recognition, and caution must be used before reaching such a conclusion. In spite of the tremendous frequency of the attacks, there is little or no mental deterioration. Pyknolepsy runs a natural course and disappears at or about puberty, as mysteriously as it came. In this it stands supreme among the epilepsies as a benign affliction.

EDITOR'S ABSTRACT.

THE BLOOD CALCIUM IN "IDIOPATHIC" EPILEPSY. R. L. HAVILAND MINCHIN, J. Neurol. & Psychopath. **17**:314 (April) 1937.

Minchin investigated the calcium content of the blood in "idiopathic epilepsy." In fifty-four cases he obtained an average value of 10.5 mg. per hundred cubic centimeters of blood. This is slightly higher than the normal values of from 9.6 to 9.9 mg. reported by other authors. The range of variations was definitely greater than that in normal subjects. Minchin explains these results by the longer rest in bed of his patients, which tends to raise the serum calcium. He found that alterations in the level of the blood sugar and in the tension of the autonomic nervous system failed to influence the values for blood calcium. He concludes that the blood calcium in epilepsy is normal.

N. MALAMUD, Ann Arbor, Mich.

PROGRESSIVE EVOLUTION OF JUVENILE DEMENTIA PARALYTICA IN SPITE OF INTENSIVE TREATMENT WITH ACETARSONE IN A PATIENT WITH HEREDOSYPHILIS TREATED SINCE BIRTH. L. MARCHAND, M. BRISSOT and P. DELSUC, Ann. méd.-psychol. **95**:93 (Jan.) 1937.

From the standpoint of clinical evolution one may distinguish two types of juvenile dementia paralytica—one "massive," leading rapidly to profound dementia and "acquired idiocy," the other slowly progressive and characterized by a selective impairment of memory and attention, with relative preservation of reasoning and judgment. The authors report a case of the second type. A boy, born at full term, had pemphigus at birth. For ten consecutive years he received antisyphilitic treatment and appeared healthy clinically. At 10 years of age he began to show signs of deterioration and at 12 had to be taken out of school. At about this age he had the first epileptiform attack. At 13 his mental age was 6½ years. Examination of the spinal fluid showed a positive Wassermann reaction, 24 lymphocytes per cubic millimeter and 60 mg. of protein per hundred cubic centimeters. Fever therapy was without effect. Neurologic symptoms and deterioration progressed. In 1933, at the age of 14 years, he began to receive treatment with acetarsone. In 1934, at the age of 15, there occurred an apparent arrest in the evolution of the disease. The tremor, dysarthria, ataxia and exaggeration of tendon reflexes subsided. However, the morbid process was not arrested, as was shown by recurrent epileptiform attacks, in one of which he died, at the age of 16 years and 2½ months. Postmortem study of the central nervous system revealed lesions of dementia paralytica in full evolution. The inflammatory process was diffuse. The pia mater was so infiltrated in places as to produce a gummatous appearance. Proliferation of the microglia and of large astrocytic monster cells, especially in the cortex, revealed a pathologic process of extreme intensity. The authors con-

clude that treatment for the slowly progressive type of juvenile dementia paralytica, resembling the disease in adults, is ineffective and that therapy for this type, as for all the other infantile encephalopathies, remains purely preventive, viz., treatment of the parents before conception and of the mother during gestation.

YAKOVLEV, Waltham, Mass.

SYNDROME OF PYRAMIDAL DEFICIENCY. J. A. BARRÉ, Rev. neurol. **67**:1 (Jan.) 1937.

Barré discusses chiefly the leg sign described by him in 1919 as an indication of deficiency of the pyramidal tract when other signs, such as reflex changes and plantar extension, are absent. He first observed the condition in a soldier who complained of fatigue in marching. On turning the patient face down and having him elevate his legs to the vertical position, he noted that there was rather rapid drooping of the leg on the affected side, even though the patient made a definite effort to maintain the posture. The posture on the normal side was maintained without difficulty and without excessive muscular contraction. A modification of this test is to have the patient flex the lower limbs strongly on the thighs when still in the ventral position, whereupon it is noted that flexion is incomplete and plantar flexion of the foot is less on the affected side. Finally, in doubtful cases the test can be tried with the patient resisting the efforts of the examiner to pull down the lower limbs from their position of flexion. The test is most instructive in cases of mild recent hemiplegia, and certain precautions must be taken in regard to pain and contracture; a real effort is needed on the part of the patient; the feet must be kept separated, and the test may be invalidated by the presence of sensory disturbances. It is almost impossible to simulate this sign of organic disease. As a manifestation of central disturbance it is important, since the affected muscles, though they may maintain a degree of tension while on stretch, do so with more difficulty when they are contracted. On the other hand, in cases in which the peripheral neurons are affected, the muscles maintain their tone better when the muscle is fully contracted.

Another test may be carried out with the patient in the dorsal position, the thighs elevated to the vertical and the legs extended horizontally, a test used by Mingazzini, in which the emphasis is on the psoas rather than on the posterior muscles of the thigh. It is less sensitive than the leg test. There is also the possibility that the Mingazzini maneuver is more affected by disturbances in the vestibulospinal tract than in the pyramidal tract.

A similar symptom of pyramidal deficiency may be elicited in the upper limbs by noting the efforts of the patient to maintain the hands at the elevation of the shoulder level, the elbows being straight and the fingers separated from one another. This posture cannot be held for any length of time by a limb in which the cortical supply is deficient, even though no other evidences of pyramidal disturbance are present.

In the face, contraction of the obicularis oculi muscle against resistance is less on the affected side. In such cases of pyramidal deficiency there may be no alteration in reflexes and no spasticity. There are apt to be hypotonus rather than hypertonus, and some reduction in the temperature of the skin. The cutaneous reflexes may even be greater on the affected side, possibly on account of hyperalgesia, which often occurs.

It is rare to find a syndrome of pure pyramidal deficiency, for usually there is spasticity as well. However, in compression of the frontal lobe it may be of singular importance and may differentiate between compression and infarction. Occasionally, in such a lesion of the frontal lobe the syndrome is found on the same side as the tumor or hematoma and is then interpreted by Barré as due to involvement of the frontal lobe by herniation of the affected side beneath the falx. The condition is occasionally seen in thrombosis or angiospasm and also after intoxication with illuminating gas or carbon disulfide.

Barré gives various methods of differentiating the syndrome of pure pyramidal deficiency and other disturbances of motor function. For instance, in parkinsonism the posture is held for a prolonged period with some effort, but there is gradual inversion of the toes on the more affected side. As regards sensory defects, Barré states that hypotonus is not caused by loss of deep sensibility but that the leg phenomenon is not infrequently found when the patient is unable to recognize the posture that is imposed on him. Barré concludes that the syndrome of pure pyramidal deficiency is more often due to compression than to destruction and that it is related to the prefrontal rather than to the frontal area, disturbances in the motor zone being more commonly followed by spasticity and other "irritative" symptoms.

FREEMAN, Washington, D. C.

ABSCESS OF THE TEMPORAL LOBE OF OTITIC ORIGIN, CURED BY PUNCTURE AND WIDE DECOMPRESSION. C. VINCENT, M. DAVID and H. ASKENASY, Rev. d'oto-neuro-opht. **15**:81 (Feb.) 1937.

It has been shown by Vincent, David and Askenasy (*Rev. d'oto-neuro-opht.* **14**:593, 1936) that it is possible to cure certain encapsulated abscesses of the brain by removal en masse without drainage and that encapsulation can be favored by preliminary puncture and wide decompression. The case reported demonstrates that in certain acute stages decompression and puncture alone may effect a cure. The patient, aged 8 years, two weeks after purulent otitis of the right ear, experienced a progressively increasing syndrome of intracranial hypertension. Seven weeks after beginning of the otitis, operation revealed a nonencapsulated abscess of the temporal lobe, with extensive collateral edema. Evacuation of the pus by puncture without incision of the dura, combined with wide decompression, caused such rapid and complete disappearance of the symptoms that it seems warranted, more than ten months after the intervention, to anticipate a definite cure. The authors believe that if in certain cases puncture of the abscess and decompression transform a subacute into a chronic, encapsulated abscess, which may subsequently be removed en bloc, a similar technic is capable in certain other cases of effecting a cure rapidly and more simply by causing resorption of the inflammatory focus without the necessity of capsule formation. The difference in the evolution of abscess after decompression is due, in large part, to a difference in the virulence of the causal micro-organisms. In the case reported the infecting organisms were the staphylococcus and streptococcus. Cerebral edema was responsible to a greater degree than the purulent collection for the intracranial hypertension. The treatment of cerebral abscess must embrace not only evacuation of the pus but, especially, control of the edema.

DENNIS, San Diego, Calif.

VESTIBULAR REACTIONS IN CHRONIC ALCOHOLISM. J. A. BARRÉ and O. METZGER, Rev. d'oto-neuro-opht. **15**:87 (Feb.) 1937.

During the past several years Barré and Metzger have studied the vestibular reactions in cases of chronic alcoholism and have accumulated the protocols in sixty cases. The cases are classified as those of marked polyneuritis, moderate or slight polyneuritis and delirium tremens and as cases in which there were no characteristic signs of polyneuritis. Study of the results of vestibular examination shows: (1) the rotation test is the first to be affected and is most profoundly modified in chronic alcoholism; (2) in a certain number of cases of generally severe involvement caloric hyporeflexia is observed, and (3) the galvanic test is almost always unaffected, even in severe conditions of long standing. The type of dissociation deserves emphasis and appears to be peculiar to chronic alcoholic intoxication. Possibly it is a manifestation of neuritis of the most peripheral vestibular nerve fibers, which would be in accord with what is known of the action of alcohol on the nerves.

DENNIS, San Diego, Calif.

Diseases of the Spinal Cord

INGESTION OF VITAMINS A, B, C AND D AND POLIOMYELITIS. J. A. TOOMEY, Am. J. Dis. Child. **53**:1202 (May) 1937.

Some cases of poliomyelitis that Toomey studied suggested a correlation between the lack of certain vitamins and resistance to poliomyelitis. Therefore he experimented on Macacus rhesus monkeys and found that the ingestion of large doses of vitamins A, B and C did not protect the animals receiving them. On the other hand, the animals that were given vitamins A, B, C and D were protected from the effect of the virus when it was introduced by way of the gastro-intestinal tract. It is paradoxical that though the lack of vitamin D makes monkeys susceptible to poliomyelitis, the rise in the morbidity of the disease occurs at the time of year when human beings theoretically should receive plenty of the antirachitic factor from the summer sun. The author has observed recently that the blood serum of eight rachitic children taken during the active stage of the disease contained no agglutinins against organisms of the enteric group, and since the agglutinin titer against enteric organisms in blood serum taken from animals in the prostate stage of poliomyelitis is practically nil, a possible connection is thought to exist between the lack of vitamin D and the lack of agglutinins against enteric organisms. When the roentgenographic evidence and the readings for calcium and phosphorus in the blood serum had become normal, agglutinins against enteric organisms had not yet appeared, their production lagging behind the other physical and biochemical signs of recovery. Since lack of agglutinins against enteric organisms makes monkeys more susceptible to poliomyelitis when the virus is given by way of the gastro-intestinal tract and since this susceptibility is further enhanced by subcutaneous injections of enteric organisms and their toxins, it is not illogical to suspect a connection between the loss of agglutinins, the susceptibility to the diseases and the lack of vitamin D. The virulence of virus preparations is decreased after exposure to ultraviolet radiation. EDITOR'S ABSTRACT.

MYELOPATHY FOLLOWING VACCINATION. CLARENCE W. OLSEN and KENNETH H. ABBOTT, Bull. Los Angeles Neurol. Soc. **2**:34 (March) 1937.

Olsen and Abbott report the case of a man aged 36 who, after primary vaccination in March 1929, suffered from severe vaccinia, with a temperature of 104 F. for a week, and numbness and weakness of the lower extremities. The weakness disappeared quickly, but the numbness persisted. He continued at work until June 1931, after which there was gradual development of further sensory loss in the lower extremities, with progressive weakness and cramping in the legs, sphincter disturbances and fatigability. Examination revealed irregular, sluggish pupils and increased tendon reflexes, with ankle clonus and pathologic reflexes. The patient became unable to walk in November 1934, and in September 1936 reexamination revealed complete spastic paraplegia, dribbling of urine, pathologic reflexes on both sides, absence of abdominal and cremasteric reflexes and sensory impairment below the twelfth dorsal dermatome. Vibration and position sense were absent in the lower extremities. Spinal puncture revealed normal serologic and dynamic findings, except for a cell count of 13 per cubic millimeter and some increase in the globulin content. Slight improvement followed this examination, but in November 1936 there were atrophy in the lower extremities without fibrillation and reduction of the tendon reflexes. Olsen and Abbott think that the onset of the disease was clinically distinctive of a form of postvaccinal encephalomyelitis but admit that the subsequent course was more in keeping with a diagnosis of acute disseminated encephalomyelitis precipitated by vaccinia. MACKAY, Chicago.

NONPARALYTIC POLIOMYELITIS VERSUS CHORIOMENINGITIS. P. F. LUCCHESI, J. A. M. A. **108**:1494 (May 1) 1937.

Lucchesi presents an analysis of the sixty-seven cases of patients with poliomyelitis admitted to the Philadelphia Hospital for Contagious Diseases from July

to November 1935. The ages of the sixty-seven patients ranged from 6 months to 26 years. There was an acute onset with fever, headache, nausea, vomiting and stiffness of the neck in most of the patients. An increased number of white cells was observed in the spinal fluid, most of which were lymphocytes. In thirty-five, or 52.24 per cent, of the patients there was evidence of weakness or paralysis, while thirty-two were without such manifestation. The author's concern is mostly with the second group of thirty-two patients, who were admitted during the same period, were treated in the same ward and presented the same symptoms as the first group but who showed no evidence of weakness or paralysis on leaving the hospital. It is natural to wonder whether in this group of nonparalytic patients one is not dealing with the same disease as in the first group, in some cases of which there was paralysis while in others there was not, or whether one is concerned with an entirely new disease. The condition might be acute lymphocytic choriomeningitis, aseptic meningitis as reported by Gunther or perhaps the epidemic serous meningitis noted by Eckstein. Even if such a diagnosis could be made in case of the thirty-two nonparalytic patients, the disease could likewise be called poliomyelitis without paralysis. The occurrence of this condition during the summer months, the type of onset, the symptoms and signs and the presence of paralysis in some cases and the absence of paralysis in others strongly favor the diagnosis of poliomyelitis. However, the absence of paralysis and the presence of a marked familial tendency may be interpreted by some as sufficient evidence against such a diagnosis. For many years the medical profession has maintained that poliomyelitis without paralysis occurs more frequently than poliomyelitis with paralysis. Paul, Salinger and Trask showed that the abortive form of poliomyelitis may be from two to five times as common as the form with paralysis. From experience in several recent epidemics, one cannot help but be impressed by the growing tendency for poliomyelitis (1) to affect the older age groups, (2) to have a lower rate of attack, (3) to cause residual paralysis in fewer cases and (4) to show a gradual decrease in the death rate. A marked familial tendency was not a prominent feature in the author's cases. Only eight cases occurred in three families. The failure to produce disease from nasal washings, spinal fluid and other tissues and the inability to demonstrate the presence of antiviral substances in convalescent serum of patients, even for virus of a known or mixed type, constitute only presumptive, and not absolute, evidence against a disease entity. Therefore, if one is to make the clinical diagnosis of acute lymphocytic meningitis, acute lymphocytic choriomeningitis or acute epidemic meningo-encephalitis in cases of the type reported here, one must deny the existence of poliomyelitis without paralysis, and no condition can safely be diagnosed as poliomyelitis unless there is evidence of weakness or paralysis. It is true that in the laboratory a virus which behaves differently from that of poliomyelitis has been isolated by many investigators, but this is of no help to the physician in practice. From the point of view of public health, it is much safer and wiser at present to handle such patients as having acute anterior poliomyelitis without paralysis. In view of the facts presented, Lucchesi believes that Philadelphia, like other districts, experienced a mild or an atypical form of poliomyelitis in 1935.

EDITOR'S ABSTRACT.

Peripheral and Cranial Nerves

CLINICAL VALUE OF SYMPTOMS OF SYMPATHETIC ORIGIN IN TUMORS AND INFLAMMATORY PROCESSES OF THE RETROPERITONEAL SPACE. E. HESSE, Presse méd. **45**:492 (March 31) 1937.

In 1929 Hesse described a triad of symptoms of retroperitoneal tumor and their influence on the sympathetic nerves of the corresponding lower limb. These symptoms are lowering of the temperature, excessive sweating and, during the period of nervous excitation, exaggerated pilomotor reflex in the lower limb on the side of the tumor. During the period of advanced destruction, when the sympathetic nerve is either inhibited or paralyzed, the temperature of the limb is again increased,

the sweating stops and the pilomotor reflexes are arrested. The symptoms described are important when the tumor is in its early stage, during which the diagnosis and localization of the growth can be made with no other methods. The difference in temperature is best measured at the toes or the back of the foot. By merely laying the hand on both feet, the difference in temperature can often easily be made out. For more minute comparisons, comparative thermometry will have to be applied. By means of this method it is possible to state whether the process is in the initial or the advanced stage. The temperatures of both limbs are traced daily, and the day on which the two temperatures are the same indicates the passage from the state of nervous excitation to that of inhibition or paralysis. Hesse named this crossing "calorimetric scissors." These symptoms were verified in eight patients, in some of whom the difference in temperature was often more than 5 degrees and easily noticeable to themselves.

EDITOR'S ABSTRACT.

CIRCUMSCRIBED ATROPHY OF MUSCLES OF THE THENAR EMINENCE AS INITIAL AND RESIDUAL SYMPTOM OF LEPROSY. N. DE SOUZA CAMPOS and P. W. LONGO, Rev. brasil. de leprol. **5**:29 (March) 1937.

De Souza Campos and Longo emphasize the importance of electrical examination of the muscles in the early diagnosis of nervous leprosy. According to the authors, all patients with muscular atrophy must be subjected to electrical examination, which is the best topographic method for the diagnosis of nervous leprosy, as well as for determining the evolution of the disease. They report five cases in which atrophy circumscribed to the muscles of the thenar eminence was a symptom, early or late, of leprosy of the ulnar nerve. From their clinical study, as well as from a review of knowledge on the anatomy of the hand, the authors conclude that in their cases only the terminal motor branches of the ulnar nerve and the interosseous posterior nerve were involved in the leprous degenerative process.

EDITOR'S ABSTRACT.

Muscular System

ORAL AND PARENTERAL ADMINISTRATION OF PROSTIGMIN AND ITS ANALOGUES IN MYASTHENIA GRAVIS. L. P. E. LAURENT and MARY B. WALKER, Lancet **1**: 1457 (June 27) 1936.

Laurent and Walker report a follow-up study of eight patients with myasthenia gravis, most of whom had been treated for more than a year. Five patients were somewhat better than a year before and had suffered no relapses. Two had had relapses from which they recovered, although prostigmin (the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methyl sulfate) was continued throughout. One patient had died; in this case there was a long history of previous attacks of dyspnea before treatment began. The patient had had two similar relapses after taking prostigmin and had died in the second, while she was no longer under the influence of the drug. The authors conclude that the treatment appears to have no direct effect on the ultimate course of myasthenia. At the same time it brings about improvement in the general health of the patient; he is able to eat more adequate meals and to lead a more varied life.

The authors found that prostigmin is active when administered orally and that from 25 to 30 mg. give a result comparable in intensity and duration with that after an injection of 0.5 mg. Abdominal pain, which is produced by large doses of prostigmin, can be prevented by giving atropine. The authors have found it helpful to give ephedrine sulfate in ¼ grain (16 mg.) doses twice a day, with prostigmin.

WATTS, Washington, D. C.

OBSERVATIONS ON MYOTONIA. W. RITCHIE RUSSELL and E. STEDMAN, Lancet **2**: 742 (Sept. 26) 1936.

Russell and Stedman state that it has become evident from the investigations of Dale that the transmission of nerve impulses to voluntary muscles involves the

liberation of acetylcholine at the motor nerve endings. In cases of myasthenia gravis it has been found that the administration of physostigmine or its analogs, such as prostigmin (the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate), produces a striking improvement in the symptoms through an inhibitory effect on the choline esterase which destroys acetylcholine. The administration of a large dose of a potassium salt has also a temporary good effect in cases of myasthenia gravis, presumably through its action in stimulating the liberation of acetylcholine. These observations suggest that in myasthenia gravis there is deficient production or delay in the liberation of acetylcholine at the motor nerve endings.

In diseases such as myotonia congenita and myotonia atrophica, on the other hand, the muscles involved in the myotonia show a striking delay in relaxation, which suggests that in these conditions there may be excessive liberation or abnormal accumulation of acetylcholine at the motor nerve endings.

In a case of myotonia congenita in a man aged 21, who had four brothers suffering from the same disease, the authors demonstrated that an injection of 1.25 mg. of prostigmin made the myotonia definitely worse. The administration by mouth of 5 Gm. of potassium chloride or 16 Gm. of potassium citrate in solution had also a striking effect in increasing the myotonia, so that within half an hour of its administration the patient was hardly able to move because of the increased stiffness. These observations suggested to the authors that in cases of myotonia congenita there is an abnormality of the mechanism by which acetylcholine is liberated at the motor nerve endings and that this abnormality is probably in the nature of excessive production or abnormal accumulation of acetylcholine. In a case of myotonia atrophica similar aggravation of the myotonia was produced with prostigmin and potassium citrate, but to a less marked degree.

The patient with myotonia congenita had observed that after drinking a pint of beer the myotonia disappeared entirely for about an hour. Russell and Stedman repeated the experiment and the patient's observation was confirmed. The myotonia in this case was much less prominent for a short time after waking in the morning.

WATTS, Washington, D. C.

ACUTE POLYMYOSITIS. W. MÜLLER, Deutsche Ztschr. f. Nervenh. **142**:162 (Jan. 18) 1937.

Müller describes two cases of acute myositis, in one of which there was a fatal termination. The disease started with slight pains in the extremities, followed after several days, or even weeks by fever. The muscular pain varied during the course of the disease. Accompanying purulent dermatitis was observed. In both cases hemolytic cocci were cultured from the abscesses and excised pieces of muscle. In the case of fatal termination there was marked eosinophilia (up to 41 per cent), but all examinations to determine the presence of parasites gave negative results. Histologic examination of the muscles showed perivascular infiltration, consisting of lymphocytes and eosinophilic leukocytes in the case in which the patient died and predominantly lymphocytes in the second. In both cases enlargement of the spleen was present. In the second there was transitory jaundice. These changes suggest that acute myositis is not a localized disease but a general infection with preponderant implication of the musculature.

ADLER, Boston.

Special Senses

PROGRESSIVE ATROPHY OF THE OPTIC NERVE IMPROVED BY THE REMOVAL OF A CRANIOPHARYNGIOMA. E. JOSEPH, Ann. d'ocul. **173**:318 (April) 1936.

Joseph reports a case of toxic retrobulbar neuritis in which there was progressive loss of vision in the left eye. In 1935 temporal hemianopia was present in the right eye and complete atrophy of the optic disk in the left. There was no pituitary disturbance. Neurologic examination gave normal results. Roentgen-

ography showed enlargement of the sella turcica. Surgical intervention revealed a suprasellar and intrasellar cystic tumor involving the left optic nerve, the caliber of which had not decreased. After histologic examination a diagnosis of craniopharyngioma was made. Twenty days after operation, visual acuity and the extent of the visual field were improved in the right eye.

BERENS, New York.

HERPES ZOSTER OPHTHALMICUS WHICH FIRST AFFECTED THE EYE. BUSSY and G. BONAMOUR, Ann. d'ocul. **173**:477 (June) 1936.

Bussy and Bonamour report the case of a child aged 7½, in whom there developed interstitial keratitis. Several days before the appearance of the herpes zoster in the region of the infraorbital and nasal nerves, folds in Descemet's membrane were observed.

BERENS, New York.

EAGLETON'S SYNDROME. F. J. COLLET and MAYOUX, Rev. d'oto-neuro-opht. **14**:727 (Dec.) 1936.

The case reported was that of a woman aged 56, who suffered a stroke in 1926, followed by paralysis of the left facial nerve. Later, violent headaches and vomiting appeared, and all the cranial nerves on the left side, except the optic, became involved. Examination revealed complete deafness in the left ear and no reactions to caloric tests. In the right ear hearing was normal, and the caloric test revealed marked reaction in nystagmus and vertigo from the horizontal canal, but no reaction from the vertical canals.

In France it is not generally admitted that there exists elective functional disturbance of the vertical canals. Hautant considered it a sign of vestibular hypoexcitability, as did Weill. Aubry and Caussé regarded it as pseudoparalysis of the vertical canals. Collet and Mayoux cannot admit that there was hypoexcitability of the right labyrinth in their case. They think the phenomenon was an elective functional disturbance of the vertical canals.

DENNIS, San Diego, Calif.

CONGENITAL DISTURBANCE OF ASSOCIATED MOVEMENTS OF LATERALITY (STILLING'S SYNDROME): CONSIDERATIONS ON THE VESTIBULAR EXAMINATION. E. AUBARET, G. E. JAYLE and G. FARNARIER, Rev. d'oto-neuro-opht. **15**:33 (Jan.) 1937.

On the basis of the study of a case of their own and of several cases reported by others, Aubaret and his associates believe that Stilling's syndrome is not always of peripheral origin. This syndrome is characterized by congenital monocular absence of movements of laterality, enophthalmos and movements of sursumvergence when the abolished function is attempted. The case reported is that of a boy aged 9 years, with congenital convergent strabismus of the right eye. There was slight enophthalmos of the left eye. When he looked to the left, the left eye did not pass the median line and the enophthalmos was increased. When he looked to the right, the left eye executed movements of sursumvergence. Convergence was made only with the right eye. The pupillary reflex in accommodation was abolished, and the reflex to light was maintained in the left eye. Vestibular stimulation by rotation produced normal responses from the right eye; in the left eye there was no nystagmus to the left. Transformation of the lateral movement into sursumvergence permits establishment of a semeiologic chain between strabismus with sursumvergent deviation in certain cases and complete paralysis of lateral movement; both conditions are congenital. If Stilling's syndrome leads by successive transitions to strabismus with sursumvergent deviation, it leads also to simple concomitant strabismus, the intermediary step being congenital paralysis of the external oculomotor nerve, with the addition of strabismus of the opposite eye. These facts support the theory of the frequent, if not constant, central origin of the syndrome. Further support is furnished by the history of certain paralyses of movement of the globe which shows that a cerebral lesion may cause signs

identical with those observed in Stilling's syndrome: oculopalpebral synkinesis and enophthalmos in cases of paralysis of lateral movements and replacement of provoked vestibular movements of laterality by movements of sursumvergence. The fact that atrophy of the internal and external rectus muscles occurs is not an argument for a peripheral lesion, for a central lesion may be followed by degeneration of the muscles.

DENNIS, San Diego, Calif.

Diagnostic Methods

THE GALVANIC FALLING REACTION IN PATIENTS WITH VERIFIED INTRACRANIAL NEOPLASMS. EDWIN J. BLONDER and LOYAL DAVIS, J. A. M. A. **107**:411 (Aug. 8) 1936.

Blonder and Davis state that Augustine in 1803 demonstrated that stimulation of the region of the ear by the galvanic current produces falling. By 1874, as a result of the investigations of Purkinje, Hitzig, Breuer and others, it had been demonstrated that closure of the galvanic circuit through the labyrinth produces anodal falling and nystagmus toward the cathode and that opening the circuit causes reversal of the direction of both nystagmus and falling. Further clinical and experimental observations regarding galvanic stimulation by Neumann, Bárány, MacKenzie, Alexander and a host of other investigators resulted in confusing and controversial evidence regarding the value of galvanic stimulation of the ear. The impression gained by many otologists was that when a small amount of current is used the stimulation is limited to the labyrinth. The contradictory clinical results obtained by galvanic stimulation of the labyrinth has caused its infrequent application. Blonder recently described a clinical application of the galvanic falling reaction by the use of a balance board, which proved to be as accurate as the caloric test and produced consistent results. The balance board consists of a platform 16 inches (40.64 cm.) wide, 21 inches (53.34 cm.) long and three-fourths inch (1.91 cm.) thick, under which was a fulcrum 3½ inches (8.89 cm.) wide and seven-eighths inch (2.22 cm.) high. The patient was placed in the normal standing position with the eyes closed on the platform of the balance board, which was arranged so that a normal patient could maintain his equilibrium without effort. Any change in the patient's center of gravity would immediately be registered by lowering one side of the balance board. Circular moist electrodes, connected to the galvanic machine, were used. For unilateral stimulation of the labyrinth, one electrode was placed on the mastoid and the other on the sternum. One hundred and fifty-four persons, including 100 normal persons, were tested for the galvanic falling reaction with the use of this balance board. Blonder and Davis arrive at the following conclusions: The galvanic falling test with the use of the balance board is an accurate, simple clinical test for determining the integrity of the vestibular postural arc. A series of 154 patients tested for galvanic falling with the use of the balance board indicated that persons with peripheral labyrinthine defects fail to react to the test. A group of patients with supratentorial tumor required, on an average, less galvanic current to produce falling than patients with infratentorial tumor. Experimental evidence obtained on decerebrated cats indicated that the galvanic current, as used with the balance board to produce falling, is not localized to the brain stem but has a peripheral action. The galvanic falling reaction appears to be a test for otolithic labyrinthine function, which the authors hope, with the accumulation of a large series of patients with defective vestibular arcs, will lead to the diagnosis of isolated lesions in the vestibular postural pathway. EDITOR'S ABSTRACT.

THE LOCATION OF CEREBRAL TUMOURS BY ELECTRO-ENCEPHALOGRAPHY. W. GREY WALTER, Lancet **2**:305 (Aug. 8) 1936.

Walter reports five cases in which electro-encephalograms were made before operation, and the region of the new growth was located correctly by the character

of the waves. He states that in cases of intracranial tumor in which the cerebral cortex was invaded by tumor and the pressure was still moderate or had been reduced, slow potential waves (of the order of from 10 to 20 microvolts and occurring at the rate of 2 or 3 per second) were led off from the skull immediately over the place where the tumor was observed subsequently at operation or autopsy. He suggests that these slow waves from the neighborhood of the tumor be called gamma (γ) waves until their true nature is discovered. "There is a possibility that the γ waves have some connexion with the evidences of pressure in the cortical area overlying a tumour and the disturbance of function and nutrition with which this state must be associated. Perhaps the most striking difference between the normal α waves and the γ waves is that the latter are in no way affected by sensory stimulation or mental activity. Unlike the α waves, therefore, they are not symptomatic of physiological rest.

"It should be emphasized that although the region of new growth has been located in the four cases attempted where it has been in or near the cortex, and no non-existent tumours have been 'located,' this method can never be anything but supplementary to the clinical and skiagraphic techniques, and is probably as liable to error as they are in some circumstances."

WATTS, Washington, D. C.

Congenital Anomalies

TWO CASES OF CONGENITAL ANOMALIES OF THE BRAIN. CORNELIA DE LANGE, Am. J. Dis. Child. **53**:429 (Feb.) 1937.

De Lange reports two cases in which occurred some of the features previously reported by her in connection with congenital anomalies of the brain, especially of the neostriatum—namely, pseudohypertrophy of the muscles, extrapyramidal motor disturbances and mental deficiency. The first infant showed muscular hypertonia, especially in the shoulder and pectoral regions. The child died of erysipelas. Autopsy showed many congenital anomalies of the brain, such as conglomeration of the blood vessels at the base of the frontal lobes, polygyria, abnormalities of the rolandic and sylvian fissures, absence of the corpus callosum, septum pellucidum and anterior portion of the fornix, displacement of several parts of the brain stem and pallidum, defective myelinization, sparse ganglion cells, hypertrophy of the paleostriatum and malformation of the centrum semiovale. There were also recent meningitis and encephalitis superimposed on the vestiges of an inflammatory process of longer standing.

The second child showed muscular hypertonia, possibly with some hypertrophy. He lay with the head hyperextended and had convulsive attacks of hypertonia of the whole body and clonic extension movements of the arms and legs. There were also abnormal grooves in the feet, hypertrichosis over the sacral region and fovea coccygea. Autopsy was not permitted, but de Lange believes that this child had a congenital anomaly of the brain.

The author denies that there is a relationship between congenital myxedema and the triad of congenital hypertrophy of the muscles, extrapyramidal motor disturbances and mental deficiency.

WAGGONER, Ann Arbor, Mich.

COMPLETE ABSENCE OF THE CORPUS CALLOSUM IN A MAN AGED 39 WITHOUT MENTAL SYMPTOMS. ADOLPH JUBA, Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:45 (Aug.) 1936.

Juba reports the case of a man aged 39 who died of anthrax. He had been employed for thirteen years in a leather factory, his work being satisfactory. He was reliable, punctual and skilful. He had attended school and acquired a degree of education about equal to that of the average person in his social stratum. He was always much interested in sports and followed the sports news closely.

Autopsy of the brain showed absence of the corpus callosum. The gyri were somewhat smaller toward the poles of both hemispheres. A large cystic structure, closed at both ends and extending anteriorly, replaced the missing corpus callosum. This cyst did not communicate anywhere with the ventricular system. The right frontal lobe was smaller than the left. The gyral pattern on this side was irregular, especially in its ventrolateral part, where pachygyric malformations were seen. The white matter in the right hemisphere was also poorly developed, with a number of islets of heterotopic gray matter. The hemispheres were adherent along the sagittal fissure. The so-called callosal longitudinal bundles (Probst) were well developed, especially on the right side. There was moderate internal hydrocephalus.

Onufrowicz emphasized that the existence of the callosal longitudinal fasciculus is one of the most characteristic features of brains without a corpus callosum. There is ample evidence supporting the theory of Probst and Sachs that this bundle is composed of heterotopic callosal fibers. Its course resembles that of the corpus callosum; the myelinogenesis is similar, and in cases of incomplete development of the corpus callosum its fibers have been noted to unite with the callosal longitudinal bundle before they enter the hemisphere. Juba adds that the most probable explanation for the anomaly is an inflammatory lesion in early fetal life, with formation of the meningeal cyst, which prevents normal development of the corpus callosum. The cyst in this case, not being in the region of the anterior commissure, did not interfere with its normal development. The diminished size of the right frontal lobe can be explained by the pressure of the cyst on the right anterior cerebral artery, thus interfering with nutrition of the part of the brain supplied by this vessel. No changes were observed in the anterior cerebral artery in this case. The author calls attention to the ability of the brain to adapt itself to the absence of the corpus callosum.

SAVITSKY, New York.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

IRVING PARDEE, M.D., *Chairman, Presiding*

Regular Meeting, Oct. 12, 1937

A SYNDROME OF MESOBLASTIC ORIGIN. DR. WALTER M. KRAUS.

A Spaniard aged 48, a fireman at the time I first saw him, was sent to my office because of an accident in 1934 which had produced a depressed fracture of the skull. He presented no neurologic sequelae of this accident, and this aspect of the case has no bearing on the symptoms which I shall describe.

After he had undressed in preparation for a neurologic examination, I was struck by the presence of marked myokymia. The muscles of the arms, shoulders and chest were in continuous motion. Since the room was not cold, I could not ascribe this to low temperature. The veins of the arms were extremely large; it was possible in some of them to see the outline of a valve. The radial and brachial arteries were tortuous and visibly pulsating. The blood pressure was 160 systolic and 100 diastolic. Roentgenograms of the skull showed considerable thickening of the carotid arteries. From a short distance I was struck by the shortness of stature and an appearance which suggested a mild form of achondroplasia. Certain muscular groups were "bellied out," giving the appearance of pseudohypertrophic muscular dystrophy. The skin was peculiarly thick, and yet hung loosely on the body, particularly around the middle. There seemed at the same time to be atrophy of the subcutaneous tissues; I could lift the skin easily and displace it several inches. This, I subsequently found, occurs in achondroplasia.

Examination of the blood disclosed: hemoglobin content, 106 per cent; color index, 0.98; red blood cells, 5,470,000; white blood cells, 8,500; a differential count of 61 per cent polymorphonuclear neutrophils, 26 per cent lymphocytes, 2 per cent monocytes, 11 per cent eosinophils and no basophils; calcium, 9.6 mg. per hundred cubic centimeters; cholesterol, 207 mg. (normal from 160 to 220 mg.), and phosphorus, 3.1 mg.

The body height was 5 feet and 1 inch (155 cm.). There were mild bilateral facial atrophy and marked arcus senilis. Owing to the patient's limited knowledge of English, I could not obtain an accurate family history, except the fact that a number of members of his family had been very short while others had been extremely tall.

Study of the literature dealing with achondroplasia, progressive muscular dystrophy, venous anomalies, arteriosclerosis and Romberg's disease (facial hemiatrophy) revealed no report of a disease or syndrome like that which I have described. I was, and still am, puzzled by the findings in this case. The clinical picture recalled progressive muscular dystrophy, but the disease was not that; it suggested achondroplasia, yet roentgenograms of the bones revealed no evidence of this condition. There was no apparent cause for the disorders of the veins and arteries.

What struck me was the multiple involvement of body tissues of mesoblastic origin—the cornea, muscles, blood vessels and subcutaneous tissues of the skin. It is apparent that, if there is any connecting link between the various disorders, a probable origin lies far back in the patient's life.

The mesoblastic tissues of the embryo are divisible early into paraxial, intermediate and lateral mesoderm. The principal derivatives of the paraxial meso-

derm are muscles, bones and subcutaneous tissues of the skin. The intermediate portion gives rise to the genito-urinary system, including the cortex of the adrenal gland. The lateral portions give rise, among other structures, to the circulatory system and the serous linings of body cavities.

As far as I could determine, this patient had no disorder of the adrenal glands. I mention this because short stature, and even dwarfism, arteriosclerosis and herculeanism are manifestations described in disorders of this gland.

A colleague with whom I discussed the case advanced, hesitatingly to be sure, the idea that the disorder might be one of the mesoblastic tissues, with evidence of changes only in the derivatives of part of the paraxial and lateral portions, unless the manifestations mentioned in speaking of the adrenal cortex may be considered to indicate partial disorder of the intermediate portion of the mesoblastic tissues.

There is perhaps a remote relation between this syndrome and the so-called lipoidoses, which Ashby, Stewart and Watkin have recently emphasized in a paper dealing primarily with chondro-osseous dystrophy of Hurler's type (gargoylism) in children (*Brain* **60**:149 [June] 1937). These authors grouped a number of diseases under the heading of lipoidoses—Gaucher's, Niemann-Pick, Schüller-Christian and Tay-Sachs disease, and perhaps Morquio's dystrophy. However, the links between these forms seem artificial, and the connection between them and the syndrome presented here seems equally artificial. More clinical and autopsy observations are needed before one can establish a sure foundation for these obscure conditions and their common factors and causes.

DISCUSSION

DR. SAMUEL BROCK: I can add nothing to Dr. Kraus' excellent clinical study. The subject, however, gives me an opportunity to discuss briefly some of the recent studies on abnormal development of tissues. Attention has been called to the loss of balance in mesodermic development which is believed to underlie such disturbances as neurofibromatosis, tuberous sclerosis and hemangioblastomatosis. Of more especial importance is the work in experimental embryology by Needham and Waddington (Needham, J.: New Advances in the Chemistry and Biology of Organized Growth, *Proc. Roy. Soc. Med.* **29**:1577, 1936. Needham, J.; Waddington, C. H., and Needham, D. M.: Physico-Chemical Experiments on the Amphibian Organizer, ibid. **27**:393, 1934). It is now known that the implantation of certain areas of ectoderm from localized, active (evocator) centers, or the dead cells from these centers or their ethereal extract, can induce the development of new, "parasitic" neural axes. Similarly, a transplanted optic cup will cause the production of a lens in various parts of the ectoderm. By other transplantations, limbs, organs or parts of organs can be stimulated to artificial growth.

According to Needham, there are a series of morphogenetic hormones operating at various stages of growth, which now and then get out of hand. These evocative substances are sterol compounds, some of which require the presence of higher fatty acids. The sterols include such complex bodies as the androgen and estrogen sex hormones, vitamin D and certain carcinogenic substances. The pronounced reparative powers of lower animals involve the use of these stimulators, e. g., the regrowth of the tail in a newt or of a claw in a crab.

Forced overripeness of the frog's ova before fertilization has also been found to produce monstrosities, secondary or parasitic embryos or even malignant teratomatous tumors, owing to disturbance in the metabolism of these sterol bodies. Needham stated that overripeness of the ova first produces abnormalities in the "sex hormones"; a more advanced state of overripeness, monstrosities, and still a later stage, teratomas and carcinogenic effects.

The significance of these "irresponsible organizers" (Needham) acting on perversely responsive tissue, whether in the neural, vascular or glandular tissues, is impressive. One is concerned here with a new dynamic physicochemical embryology, which may well hold the secret of what causes not only the fixed tissue

deviations observed in Dr. Kraus' case but the anarchy seen in various tissues in later life which leads to the formation of benign and malignant neoplasms.

DR. CHARLES DAVISON: The case reported so vividly by Dr. Kraus is the first of its kind I have seen; I believe that the disturbance may possibly be grouped with the muscular dystrophies. Whether it approaches pseudomuscular dystrophy or dystrophia myotonica is difficult to determine. Dr. Kraus' attempt to classify this disease on an embryologic basis, although worthy, has its shortcomings. In many cases of pseudomuscular dystrophy and dystrophia myotonica, there is not only involvement of muscles but implication of the endocrine glands and neural structures. This is especially true of dystrophia myotonica. I wonder whether in Dr. Kraus' case the disturbance is not in the neurohormonal system, a metabolic disorder affecting in this instance the blood vessels and muscles. Because of this, I do not know whether one should classify this and similar cases on a strictly embryologic basis or whether it may not be better to wait until more is known about the cause of the disease and classify it accordingly.

DR. THOMAS K. DAVIS: Has Dr. Kraus looked on the disturbance in this case, with respect to its cutaneous and subcutaneous features, as the clinical opposite of scleroderma? That possibility came to my mind. Perhaps such comparisons are too artificial to be useful, but this case suggests such a clinical contrast. Dr. Kraus mentioned the possibility that the muscular changes are dystrophic. Since dystrophy and scleroderma have a tendency to occur together and since the subcutaneous changes in this patient are the opposite of those in scleroderma, one would not expect the muscular involvement to be of the dystrophic variety. On the other hand, with myokymic features, amyotrophic lateral sclerosis comes to mind. Incidentally, the patient is excessively muscled, and I have never seen amyotrophic lateral sclerosis in any other type of person. I wonder if, in the end, there will not be a syndrome of amyotrophic lateral sclerosis.

DR. WALTER M. KRAUS: I wish to thank Drs. Brock and Davison for their discussion. In answer to Dr. Davis: I had not thought either of amyotrophic lateral sclerosis or of scleroderma. I have not the impression that this case represents such a clinical opposite as Dr. Davis has suggested.

BRAIN METABOLISM DURING THE HYPOGLYCEMIA TREATMENT FOR SCHIZOPHRENIA. DRS. HAROLD E. HIMWICH, Albany, N. Y., KARL M. BOWMAN, JOSEPH WORTIS and JOSEPH F. FAZEKAS, Albany, N. Y. (by invitation).

Fifty-three observations were made on 11 patients with schizophrenia, 1 with psychoneurosis and 1 with depression. Before insulin was injected the average utilization of oxygen was 7.04 volumes per cent, and that of dextrose, 12.5 mg. per hundred cubic centimeters. In 9 examinations the patients who were given injections of insulin exhibited in the precomatose condition an average uptake of 6.19 volumes per cent of oxygen and 7 mg. of dextrose. Under these conditions the arterial dextrose varied from 13 to 37 mg. per hundred cubic centimeters, and it should be remembered that a value of from 8 to 11 mg. represents substances which are not dextrose. Twenty-six observations made during coma disclosed a further reduction in utilization of oxygen to 3.07 volumes per cent and in that of dextrose to 4.16 mg. per hundred cubic centimeters. The arterial dextrose levels in these observations varied from 8 to 33 mg. per hundred cubic centimeters.

The diminished utilization of oxygen by the brain during insulin hypoglycemia discloses in a crucial manner that the chief, if not the only, foodstuff of the brain is carbohydrate, for the decreased oxygen uptake can be explained by the diminished absorption of dextrose. The decreased oxygen consumption during intense hypoglycemia cannot be ascribed entirely to the minimal absorption of dextrose and lactic acid from the blood but may be imputed to utilization of cerebral glycogen. In addition, it should be noted that there is an increase in the alkali reserve of the blood as it passes through the brain and that there is no change in esterase activity as a result of intense hypoglycemia.

The neurologic manifestations occurring during hypoglycemia are dependent on the biochemical changes. With depression of cerebral metabolism are associated symptoms first of excitement of the central nervous system and then of depression. Sweating, extensor spasms and motor activity and the Babinski sign all appear with greater or lesser diminution in cerebral uptake of oxygen. Deep coma and areflexia, however, are constantly associated with a greatly diminished utilization of oxygen by the brain.

The present studies reveal that the mental activities, like the neurologic, are dependent on brain metabolism, for the effects on the mental functions parallel the reflex changes. In this manner, the pathologic processes of schizophrenia are also affected, probably being both released and depressed with the normal functions. However, the mechanism whereby these processes are restored to normal is not disclosed.

DISCUSSION

DR. HERBERT S. GASSER (by invitation): In opening this discussion I should explain that I do so as an outsider. The field is not one in which I have worked personally. I have never seen the insulin treatment for schizophrenia, nor have I engaged actively in study of the metabolism of nerve tissue. Therefore I shall take advantage of my detachment to make some general comments that may be commonplace to those closer to the subject. The point that appeals to me is the hopeful turn which has taken place in the study of a disease which previously had none too brilliant an outlook. One can derive satisfaction from the fact that the subject is now opened, so that there is possible a physiologic analysis, such as Dr. Himwich and his colleagues have given tonight. It is demonstrated with greater clarity than ever before that the large group of patients with schizophrenia, who present the major problem of medical science today, have still within themselves the mechanism of normal reactions, ready to be brought out, if only one knows how to do it. One may perhaps look forward to future discussion on the best way to bring about restoration.

There are many aspects of this paper to be discussed. I shall take up one. Dr. Himwich dealt with the relation of function to oxidation. The point, I think, was well taken. That oxidative energy must be supplied continuously to keep the neural mechanism intact is well known. In addition, as Dr. Himwich pointed out, if oxidation falls off slightly, stimulation takes place. If it falls off more, depression supervenes. Interestingly, it was reflection along these lines which, a number of years ago, resulted in the earlier, but less successful, demonstration that schizophrenic patients may be made accessible to their environment through chemical intervention. The subject of oxidation was one which interested my friend and teacher Dr. A. S. Loevenhart, of the University of Wisconsin. As a result of this interest he was led to study cyanides, for, as is known, the basis of the effects of cyanides is a depressing action on the respiratory ferment. One of the specific effects is that on respiration. It is now known that this takes place through the intermediation of the carotid body, but at that time the action was supposed to be directly on the respiratory center. Dr. Loevenhart and his colleagues were examining the effects of cyanides on human subjects. One of the subjects, a hospital patient with schizophrenia, after the injection talked and made statements which were later verified, although he had not spoken since his admission and no history had been obtained from him. This was in 1916. The problem lay dormant until 1928, when it was again taken up. This time, in view of the difficulty of handling cyanides, use was made of another respiratory stimulant, a high concentration of carbon dioxide. With the result of these observations all are familiar (Loevenhart, A. S.; Lorenz, W. F., and Waters, R. M.: Cerebral Stimulation, *J. A. M. A.* **92**:880 [March 16] 1929).

In a broad view of the subject, the connecting links between the several methods which have been tried in the treatment for schizophrenia must be considered. If, now, attention is confined specifically to the two methods which have been mentioned, the question arises: What is there in common between the transient effect of a high concentration of carbon dioxide and the much more prolonged effect

of a series of shocks with insulin? If one assumes, as I think Dr. Himwich did, that insulin acts through some interference with the oxidative mechanism, the problem is: What relation is there between the effect of a high concentration of carbon dioxide and the state following low oxidation? Here is a point where the physiologic laboratory can interpose an observation on the electrical reactions of nerves. (I may say that the physiologist looks on a nerve as giving a qualitative indication of what the central nervous system does under given conditions.) A nerve exposed to a high concentration of carbon dioxide behaves in its electrical reactions like one that has been asphyxiated and allowed to recover. This means that the cycles of excitability are also similar.

The observation is mentioned not because it has any immediate importance but because there are probably contacts between the clinical and the laboratory observations other than the chemical relation described by Dr. Himwich and his colleagues. In other words, the study of schizophrenia is now entering on the course that has been taken in the investigation of many other diseases in which great progress has been made, with the clinic suggesting problems to the laboratory and the laboratory, in turn, making suggestions to the clinic. That is the reason that I remarked at the outset that a hopeful turn seems to have come in the study of this subject.

DR. S. BERNARD WORTIS: Some aspects of the mechanism of hypoglycemia have been presented here, but nothing has been learned of the mechanism of schizophrenia. Something has been said of what hypoglycemia does, but nothing of what schizophrenia is. Neuropsychiatrists should keep this distinction clearly in mind. Furthermore, these studies have shown that the reactions of the schizophrenic patient to hypoglycemia are not characteristic of the illness. As Dr. Himwich has said, they do not differ from those of patients with various other psychiatric and neurologic diseases, such as dementia paralytica and epilepsy. However, that does not preclude the fact that insulin therapy is helpful in selected cases, and these studies will give more information concerning effective means of therapy for the schizophrenic syndrome.

Several other interesting features appear in this paper. Dr. Himwich reported, for example, that 40 units of insulin was required for an effect which he could measure physiologically (i. e., brain metabolism) in the human being. With these data how can one explain the good effects in some patients with schizophrenia who had not received this amount of insulin? The question requires further investigation. Perhaps one explanation is that the level of sugar in the blood is not an accurate measure of that in the brain. Furthermore, insulin causes a decrease in the absorption of dextrose and its oxidation by brain tissue. I showed Dr. Himwich some of the figures for these changes I obtained with the Warburg machine in 1932. Insulin reduces the oxygen consumption of brain tissue in vitro as well as in vivo (Wortis, S. B.: *Am. J. Psychiat.* **93**:87 [July] 1936). I wonder, however, whether Dr. Himwich has made studies of the oxygen consumption of the brain after termination of the hypoglycemia in order to determine whether or not oxidation in the brain is increased beyond the normal after insulin therapy. I suspect that he would find this effect; if he does, it is an important bit of evidence. It should be emphasized that Dr. Himwich's findings show that there is little correlation between the level of the blood sugar and the clinical condition of the patient. This shows how varied must be the response to changes in brain metabolism. There is no doubt that large doses of insulin deprive the brain of its chief food substance and reduce brain metabolism. I wonder whether Dr. Himwich has made simultaneous studies of the lactic acid metabolism. I found that as the blood sugar level falls with hypoglycemia the lactic acid content of the blood rises; there is some evidence that the brain can utilize lactic acid as a food. Sugar is the brain's main fuel, but in conditions under which sugar is not available lactic acid can be used. A pointed observation was made by Eric Holmes, who has done a good deal of work on metabolism of brain tissue. He showed that cerebral anoxemia causes an increase in impulse firing by the cerebral tissue. This effect has recently been confirmed by work of Dr. Hallowell

Davis, who showed that hypoglycemia or cerebral anoxemia from inhalation of carbon dioxide or other causes produces an increase in firing of brain impulses, as seen in the electro-encephalogram. Many substances can diminish or affect the carbohydrate utilization of brain tissue, and very likely many substances will eventually be used in the treatment of what is called schizophrenia. For example, metrazol and camphor are known to help in some cases of schizophrenia in which insulin does not help. The use of insulin, metrazol, camphor, inhalation of carbon dioxide, amytal narcosis, etc., may help to divide the syndrome of what today is called schizophrenia into several more distinctly recognizable syndromes. Each of these syndromes has as its basis a specific biochemical disturbance.

One should, moreover, remember that in the field of brain metabolism the surface has only been scratched. When one recalls that nothing is known of the exact role of specific proteins, lipoids, minerals or enzymes in brain metabolism, one realizes that this is uncharted territory. At present about twenty enzymes have been isolated from brain tissue, and nothing is known of the exact psychophysiologic function of any of them. Much research work is needed in the field of psychochemical relationship. For example, one can still ask: What is the effect of psychotherapy? Many schizophrenic patients are cured by psychotherapy, or even by "judicious neglect." What effect has such therapy on brain metabolism?

Perhaps the most important gain from a study of this kind is that the entire subject of schizophrenia may some day be further elucidated. Further biochemical and metabolic studies of brain function, with more knowledge of psychochemical relationships, are needed to learn how each enzyme system in the brain works, what effect it produces on the patient's thinking and how one can alter derangements in the biochemical functions of the brain when they are present.

DR. KARL M. BOWMAN: I shall discuss this paper not on the basis of the actual findings, which speak for themselves, but from a somewhat different point of view. The paper brings out strongly the need for further researches in this field and the fact that if this problem is to be covered in an intelligent manner institutions must be more endowed with money and qualified personnel to carry out research of this sort. This paper demonstrates how research can be carried out through cooperation of men of different backgrounds and training, and even from different medical schools. In the past, psychiatrists have gone to the pathologist, the biochemist, the neurophysiologist and others for help, who in general have been friendly and kindly in their attitude but have not given much practical assistance.

Because there were available the services of a physiologist with special training in neurology who was interested in this problem, it became possible this summer for two medical schools, the Albany Medical College and the New York University College of Medicine, to combine on research in this problem at the Bellevue Hospital. Too little use is being made of the wealth of material in psychiatric hospitals; I hope that this paper will stimulate further combined researches of this type. Practically all psychiatrists lack the requisite biochemical and physiologic knowledge to supervise the laboratory work in a study of this kind. Highly competent and well trained men from other fields are needed to work on a cooperative basis.

DR. E. D. FRIEDMAN: As often happens in medicine, an empirical approach to disease is made by a courageous soul, and it becomes the task of those who follow him to seek out the physiologic processes and mechanisms which underlie what was apparently a brilliant thought. In the presence of Dr. Sakel, I hesitate to say too much. He has already hinted at some of the mechanisms which lie at the basis of the results achieved with his method of therapy. I have had occasion to follow some of this work casually, and in two instances a little more thoroughly; it has occurred to me that I may expand a little on the mechanisms involved. I do this with all due modesty.

The effect of insulin seems to be, as Dr. Himwich has demonstrated, a reduction in the entire metabolism of the brain. There are indications during this phase that the vagus nerve begins to dominate the scene. One notes, for example,

vomiting, sweating and bradycardia—evidences of increased vagal tone. Dr. Sakel has spoken of vagotropic effects and the use of insulin to paralyze adrenal activity. I wish to expand on this vague concept and to stress the neurophysiologic mechanisms involved. The vagus nerve is the regulator of anabolism, the great conserving force in human economy. It dominates in hibernation states, when the vital forces must be husbanded—witness the bradycardia, low blood sugar and lowered metabolism in these states. It counteracts the effects of sympathetic domination, in which all the fighting resources of the body are mobilized for defense, as has been pointed out by Cannon.

Insulin treatment, therefore, is a form of protective therapy. It seems that the effect of insulin is to reduce the tempo of the whole vital process in a person who is battling with all sorts of complexes, panics and threats to the ego, with consequent mobilization of all the resources of defense, in a struggle which results not in success but in the patient's becoming ill. The effect of insulin, then, is to spare these fruitless expenditures of energy and protect the patient against this fitful, anarchic discharge of energy.

This method of therapy is also protective on the psychic side. It is a form of necrosis therapy, with blotting out of the abnormal activity of the mind consequent on the states of panic and threats to the ego already spoken of. These are held in abeyance because, so far as is known, in the well developed narcosis no psychic processes go on and the person in this state is spared the necessity of thinking about his problems. This may explain the favorable effects of sodium amytal narcosis reported from so many sources. As a result of blotting out the abnormal activity of the mind, the organism recuperates, and, owing to the inherent factors of safety in the human organism stressed by Meltzer and others, the patient returns to the problems of living with a fresh approach and begins to function anew.

The fact that some of the mechanisms to which I have referred may be at play is suggested by the bizarre electro-encephalograms of the schizophrenic patient, which are simply an index of the abnormal activity of the nerve cells. I am interested to know whether any electro-encephalographic studies were carried out before the induction of therapy and were followed by studies after recovery. It would be extremely interesting to compare these graphs.

It is always dangerous to cite a single case in support of one's thesis, but I shall make brief reference to one in my experience. I had under observation for almost two years a young woman who was definitely schizophrenic and for whom the prognosis seemed utterly bad. After three months of insulin therapy she made a complete recovery. It is now about six weeks since recovery was established. The patient has complete amnesia for the entire episode of her illness, from the time of admission to the hospital up to the period at which recovery began. This may be interpreted as a self-induced protective mechanism operating on an unconscious level to blot out an unpleasant past.

Therefore, one should welcome this approach to psychiatric problems. As an organicist, I particularly welcome it because it is time to realize that there is no single approach to the human mind. The human mind is a complicated mechanism. It has many avenues of approach. The function of the involuntary nervous system and the endocrine glands cannot be minimized. They play a role which is commensurate with any psychic mechanism that has ever been suggested. A form of therapy which is based on sound and well known neurophysiologic mechanisms and alterations in the biochemical reactions of the nerve cell is a distinct step forward in an approach to mental illness.

DR. HAROLD E. HIMWICH: The observation made by Dr. Gasser that with carbon dioxide there is depression of nerve metabolism is of great interest. The possibility arises that in alleviation of schizophrenia by inhalation of carbon dioxide there may be depression of the cerebral metabolism, as there is during hypoglycemia. Dr. Wortis emphasized the importance of studies with the Warburg apparatus. No physiologic attack on the problem should be neglected, and much is to be gained from the Warburg studies. Dr. Wortis presented some interesting

studies in which he found that metabolism of brain slices from hypoglycemic animals was depressed. He also demonstrated that in the presence of dextrose the oxygen consumption of these slices rose to levels above normal. Surely, facts like these must be of significance.

In regard to dosage: Patients display individual variation in sensitivity to insulin. We first observed our effects with a dose of 40 units of insulin. In a larger series we should probably find effects with smaller doses. There is no doubt that the brain can oxidize lactic acid, as it does alcohol, in small amounts. However, unless there has been an epileptiform convulsion, the lactic acid in the blood never rises high, and therefore little is used by the brain for energy.

I wish to thank Dr. Friedman. In a brief discussion it is impossible to bring out all the physiologic changes involved in hypoglycemia. I am glad, therefore, that he discussed the action of the vagus nerve and the possible influence of rest on the central nervous system.

In conclusion, I wish to emphasize a remark made by Dr. Bowman. He pointed out that in this study we did not arrive at the cause of schizophrenia. I wish to add that an investigation of this nature can be regarded only as a beginning. We have studied some of the most accessible physiologic variations to be observed in this condition. I do not imagine for a moment that we have come to the final chemical and physiologic changes which may be associated with the causes of this disease. Only future studies can explore the vast field which is still open.

METABOLIC STUDIES DURING INSULIN HYPOGLYCEMIC SHOCK THERAPY. DRS. MEYER M. HARRIS, JOSEPH R. BLALOCK AND WILLIAM A. HORWITZ.

The chemical changes in the blood occurring during treatment with insulin hypoglycemic shock were studied in a group of 13 patients. Three of these patients were not given insulin and served as controls. The dose of insulin varied from 40 to 200 units, depending on the amount necessary to produce the desired state of coma within approximately four hours.

Venous blood was examined quantitatively for the following constituents: sugar, amino-acids, potassium, sodium, calcium, inorganic phosphorus, cholesterol and serum protein. Examinations were made before administration of insulin and one, two and approximately four hours thereafter.

Significant decreases were observed in the levels of sugar, amino-acids, potassium, inorganic phosphorus and serum protein in the blood after the administration of insulin. The levels of sugar and amino-acids remained depressed throughout the four hour period. Inorganic phosphorus was at its lowest level in the two hour period and usually rose to the original level in the four hour period. In some cases potassium was at its lowest level in the two hour period and then tended to rise. In other cases the potassium level remained markedly lowered at the end of the four hour period. In the last group the patients appeared to react more severely to insulin hypoglycemia. The possible significance of these chemical changes is discussed.

DISCUSSION

DR. NOLAN D. C. LEWIS (by invitation): I shall attempt to sum up the attitude of the Neurological Institute and bring to attention some of the aspects of this problem. Nearly a year ago, at a meeting of this academy (ARCH. NEUROL. & PSYCHIAT. **38**:188 [July] 1937) the then early studies on insulin therapy for dementia praecox were discussed, and the hope was expressed that as the results with the therapy were on the whole remarkable, the subject deserved an evaluation which only application of the scientific method can afford. There are now, according to my last survey, seventy-three publications on the insulin treatment, distributed through the literature of ten languages. The majority of these reports consist of loosely expressed ideas, optimistic descriptions and often unjustified criticisms, not uncommonly based on lack of psychiatric experience and knowledge of the great variety of clinical features of dementia praecox. On the basis of what

has been written and experienced and of what has been brought out tonight, the following pronouncements seem justifiable: First, the results show that in a relatively large percentage of cases the clinical aspects of this disorder can be favorably influenced, at least for a time. Second, in some cases the disorder is not favorably influenced but continues as before. Third, there is a fairly wide variety of physiologic reactions to the therapeutic procedure, apparently dependent not always on the inherent individual integrations of the patient but on the technic of the physician. Fourth, these studies have brought to mind the possibility of a reversibility in some of the physiologic or pathophysiologic processes underlying dementia praecox. However, it should be remembered that evidence of this reversibility or possibility of change, whatever the pathologic basis of the condition is, has long been in existence and that "shock" is able to produce this reaction. Any situation that brings a schizophrenic person near death may relieve him of his symptoms, at least temporarily. On the one hand, a major operation or appendectomy, or even repair for hernia, has produced a short, or sometimes long remission, and, on the other, similar operations have precipitated dementia praecox in what seemed to be predisposed persons. The same may be said of shock from physical trauma, to say nothing of inhalation of carbon dioxide and oxygen. Shocks of various types may produce remissions in dementia praecox or may precipitate the psychosis in predisposed persons. I mention these special or possible effects of shock not to compare their efficacy with the action of insulin but merely to emphasize that this reversible reaction is produced at times with other mechanisms for shock. Perhaps therefore, the common factor here is a metabolic disturbance. However, the effect of shock may be entirely psychologic. I see at least no evidence to the contrary at present, for psychogenic or emotional processes can produce disturbed metabolism in the body. There is a great deal of evidence for this. As a simple example: One may be healthy and ready for a square meal, when the receipt of a telegram bearing bad news may cause loss of appetite, accompanied by other striking bodily changes for several days. From emotional causes the metabolism may be upset considerably in a few minutes. However, I am not holding a brief for either side of the question but am merely pointing out some observations. One wonders whether in persons who are on the borderline and are branded psychiatrically as predisposed to dementia praecox, a shock with insulin would produce the psychosis. Or would it fortify the subject against future trouble? Some of the pathologic processes may be reversible, others not. Although interesting changes in the sugar, amino-acids, potassium, inorganic phosphorus, cholesterol and serum proteins of the blood are associated with the insulin situation, the degrees of change are not always dependent on the size of the dose of insulin administered; moreover, it is not yet possible to translate these changes into terms of a psychosis, as the other discussants have already pointed out.

In psychiatry there are four major questions. First, why does the patient have a mental disorder at all? Some have mental disorders, and some do not. Second, why does the disorder appear at a particular time in a given person's life rather than at another? Third, why does a given person have a particular type of mental trouble; that is, why are there different patterns of disorder? Fourth, what is the meaning of each symptom in the pattern? So far, insulin has not helped to answer these questions. However, there have been favorable therapeutic results. Anything that administers help is an important advance in this extensive medical problem. Dementia praecox is an extremely heterogeneous disorder. Therefore, there are needed intensive studies in the life history of the patient and the development of the psychosis, careful accounts of the mental reactions during the treatment and a long follow-up period, with the facts concerning the postinsulin results. I should like to see compared in a complete longitudinal study even five cases in which there was recovery and five in which the treatment failed. Comparison of the present blood studies with similar ones made on persons with neuroses and psychoses other than schizophrenia when placed on the insulin regimen might afford instances which would serve as leads for research. I think it would be of value if these studies could be extended to other types of reactions and

persons, in order to see whether there are differences; that is probably one of the next steps in research. One could ascertain through such studies whether there are any reactions characteristic of schizophrenia.

In a disturbance which from direct observation seems as profound as the insulin shock, it should not surprise one to find alterations in brain metabolism and in the various constituents of the blood; one would like, however, to know what they mean in terms of metabolic rearrangement and reconstruction. Is the treatment merely palliative and carried out at the risk of permanent damage to the brain? There is published evidence that damage to the brain occurs in some persons at some stage of treatment with insulin, which indicates the need for additional research in this part of the field.

Aid organized by the Federal Government and other sources is available for the study of five diseases: cancer, syphilis, poliomyelitis, malaria and yellow fever. Dementia praecox is not included; yet it destroys more persons and careers than all the others together. Therefore the information presented here amply justifies the use of a new method in a complex and, in part, intangible condition—the most difficult medical problem of the age.

Dr. Sakel should be elated at having been able to initiate so much new research, regardless of what the final results may be, and to bring so many other types of investigators into the psychiatric field. Mental disorders, of which dementia praecox is a prominent representative, are apparently on the increase. Whether the increase is absolute or relative I do not know, but there are more cases on record in the hospitals year by year. Workers in chemistry, physiology and other fields must become interested for their self-preservation. The increase in mental disorders will soon begin to threaten the very existence of mankind.

The final value of this treatment, however, remains to be seen after a period of rigid investigation and control. It makes me happy to see the beginning of important studies which will give the final opinion concerning this remarkable series of phenomena.

Dr. Manfred Sakel, Vienna, Austria (by invitation): The papers read this evening and the reports on results in Europe and the United States will, I hope, justify my efforts to introduce a physiologic basis into the treatment of psychoses. I am happy to see that my effort has found excellent soil in America. I am in the position, therefore, one year after the introduction in this country of a physiologic shock treatment, not only to listen this evening to reports of good therapeutic results but to hear that attempts are being made to search for the possible cause of the illness.

The paper by Drs. Himwich, Bowman, Wortis and Fazekas is important and represents a promising step forward. In regard to the contents: I should not dare to discuss them after analysis by a trained specialist, but the possibilities which are opened seem important.

When the facts are taken at face value, one should begin to have insight into the mystery of the development of thought. It would be well, however, to emphasize the need for caution against the mistake of taking too exclusively one point of view. It would lead too far to assume that the latest development in man, the mind, is a simple chemical process. I should say that the chemical process is a basic condition. It is the foundation of every being, but in the development of the human mind one must find transformation of energy of the most complicated type—from chemicophysiologic to mental. The link between the organic and the psychic part of the human being is the vegetative nervous system—this must not be forgotten, for in the same way that the vegetative nervous system can translate organic experience into mental response it can transform psychic stimuli to pathophysiologic expression and vice versa, in a vicious cycle. From this point of view, one should treat a psychosis as the expression of a biophysical condition, both mental and pathophysiologic, or as a psychobiologic entity in Adolf Meyer's sense.

The greatest advantage of the physiologic insulin shock treatment is that it demands of the psychiatrist in whose hands lies the management of the treatment knowledge, in the best sense, not only of internal medicine and physiology but of psychiatry.

Many physicians believe that treatment can become of general use only if it is easy and simple. Certainly this is desirable, but of secondary importance. In choosing a treatment, one must think of the good of the patient rather than of that of the physician.

In regard to further therapeutic developments, especially in treatment for resistant forms, I refer to the recent report of the Swiss congress. This evening is not dedicated to therapeutic and clinical discussion.

If the collaboration of the psychiatrist and the physiologist proves of value, it may be a step nearer realization of the dream not only of potential but of kinetic influence on psychosis. If this is achieved, it not only will be of great value to the patient but may also influence the behavior and wants of man.

In conclusion, the changes in carbohydrate metabolism in the insulin shock treatment for psychoses are not, I think, the only factors involved in the effect of this treatment. Others in all probability have a therapeutic influence. For example, the simple shock to the cell or to the vegetative nervous system and water mineral metabolism should not be forgotten. As Dr. Wortis pointed out, one may see remarkable improvement before signs of shock develop and before the dose is increased. I am sure that in these cases the blood sugar is also very low but that the brain is not sufficiently affected for coma to develop. On the other hand, Dr. Wortis said that some patients improve merely from shock with metrazol. The treatment is complex and can work from different angles. Shock with convulsions may produce recovery, or there may be coma with no convulsions, and yet recovery. The assumption that everything depends alone on changes in sugar metabolism is too simple. Drs. Himwich, Bowman, Wortis and Fazekas pointed out that before depression of the brain there is increase in activity or irritation. It is not so in all cases. I should not compare the irritation in this situation with the effects of alcohol, for I think the mechanism is different. The combustion of carbohydrates can be increased in these cases before there is depression of brain metabolism from lack of fuel. There is increase of function in some parts of the brain at certain times during hypoglycemia because not every part of the brain has the same sensitivity to insulin at the same time. It is possible that insulin, in addition to its hypoglycemic effect, has a direct influence on the vegetative nervous system, and possibly an indirect influence by increasing the carbohydrate combustion in certain portions of the brain. It would not be surprising, for example, to find that the combustion of sugar is diminished in the cortex and increased in the lower centers at certain times. This would explain the increased action in the vegetative nuclei. It may be that the cortex is not the primary organ of the human being. It might be assumed that it is an organ which is influenced by, or the functions of which are subject to, the vegetative nervous system in the same way as are all other organs of the body, such as the stomach. The vegetative nervous system regulates directly or indirectly not only the sugar metabolism but other chemical changes, which Dr. Harris reported. That the sugar metabolism is of especially great importance may be seen in my recent experiments with old conditions, in which I kept the patients in coma for nine hours or more with small doses of sugar administered at intervals. (The technic for this procedure has, however, not yet been worked out.) These patients have shown marked changes after such prolonged coma, with remarkable improvement. The significance of prolonged deprivation of sugar is shown by the fact that these patients did not respond to orthodox shock treatment until the special procedure was tried. There is no doubt in my mind that in these cases the sugar metabolism has something to do with the aforementioned changes. The procedure consisted of giving the patients their customary individual shock dose and then small amounts of sugar periodically at the point at which irreversible changes would appear. The amount of sugar administered is about a tenth of the dose ordinarily required to neutralize the entire insulin effect. The patient awakens for a few minutes, and his breathing improves; if he shows no further signs of danger, I allow him to be in coma again for about three hours and then give

him a little sugar. Although I kept these patients in coma for up to ten hours, no damage was done. These experiments indicate that the sugar metabolism is an important factor in the treatment.

DR. MEYER M. HARRIS: I wish to thank Dr. Lewis for discussing this paper. Dr. Sakel and Dr. Lewis have both indicated the complexity of the problem with which we are dealing. What we have attempted certainly has not given us any insight into the psychopathology of the disease, nor was that the purpose of the study. It was hoped, however, to gain information regarding physiologic changes which take place during this therapeutic procedure. This, it was thought, might disclose important differences between patients and yield information regarding physiologic mechanisms which would give leads for further investigations.

PHILADELPHIA PSYCHIATRIC SOCIETY

FREDERICK H. ALLEN, M.D., *President, in the Chair*

Regular Meeting, Nov. 12, 1937

AN INTERESTING RESULT WITH METRAZOL. DR. ROBERT A. MATTHEWS.

W. F. first came under attention in July 1934, when he applied for treatment at the Institute of the Pennsylvania Hospital. He was seen at that time by Dr. Francis Braceland. According to the history given by his wife, the illness had begun four months previously, when he became extremely nervous, had attacks of cardiac palpitation and expressed numerous hypochondriacal ideas. The patient expressed fear with reference to his physical condition but was not communicative. His intellectual level did not appear to be high. Physical and neurologic examination gave essentially normal results. A diagnosis of psychoneurotic depression was made.

The patient was not seen again until the spring of 1935, but there had been slight improvement in his condition during the intervening months. However, he still had a number of physical complaints and a moderate degree of depression. Investigation of the environmental situation and emotional problems revealed conflict between his wife and parents, the patient apparently not having been emancipated from the home and yet feeling a strong sense of duty toward his wife. He was placed under a therapeutic regimen consisting of oral administration of hematoporphyrinhydrochloride (photodyn) and small doses of phenobarbital. At the time of the patient's next visit his wife reported considerable improvement, but the patient's subjective complaints remained the same. I saw him for the first time in July 1935, when he was again brought to the clinic by his wife, who stated that he had been doing well until about two weeks previously, when he became more seclusive and seldom left the house. He was unable to sleep on retiring, but remained in bed until noon of the following day. The patient at that time appeared definitely retarded; there seemed to be blocking. Questions were answered after considerable hesitation; attention was poor and difficult to hold. There were little spontaneity and numerous hypochondriacal complaints. The emotional state was one of apathy. I could detect no actual depression.

The patient was not seen at the clinic from July 1935 until February 1937, when he again returned for treatment. According to the history for the interval, his condition had remained much the same during the intervening months. Dr. Reynold Jensen, who then examined him, stated that the patient was restless and apathetic, showed blocking at times, complained of black spots before the eyes, thought his legs were wasting away, claimed to have no power in the lower extremities and stated that he had pains radiating up the back and into the neck.

There was complete loss of interest in pleasurable experiences and indifference to responsibility. His wife felt that he had grown progressively worse; she stated that his personal hygiene had become poor and that he refused to change clothes, bathe or shave. He constantly looked at himself in the mirror to note any changes in his appearance. At times he appeared confused; when he attempted to wait on customers in a small candy store which his wife runs, he forgot where the stock was located. Dr. Jensen was of the opinion that there was much to suggest schizophrenia.

Again he was lost sight of for a time, but in September 1937 he applied for treatment at the psychiatric clinic for adults at the Jefferson Medical College Hospital. At that time he appeared to be extremely ill and was mildly agitated; he thought he was losing his mind and that he was going to die; he said that he could not get his breath. Things became black around him, and he complained of intense pain in the head. His father, who accompanied him, insisted that there had been no noteworthy change for the better at any time since onset of the illness, almost four years before, and that in recent months he had become a great deal worse. He wanted something to be done to alleviate the condition.

As nothing definite had been accomplished through treatment up to this time and there seemed to be no possibility of carrying out intensive psychotherapy or evidence that such treatment would benefit the patient, it was decided that something more drastic must be done. The patient was referred to the psychopathic department of the Philadelphia General Hospital on September 9 and remained until October 10. During that period he received seven doses of metrazol and had five generalized convulsive seizures. The doses of metrazol ranged from 0.6 to 0.8 Gm., the smaller dose being ineffectual. After the first few treatments there was marked improvement in the patient's condition. The hypochondriacal ideas disappeared entirely; he became more alert, helped about the ward and expressed a desire to leave the hospital and return to work in his father's feed store or his wife's candy store. When seen at that time he said that he "felt fine," considered himself entirely well and seemed in good spirits. When asked what he thought of the treatments, he replied: "Say, Doc. they're some treatments; they knock hell out of you." He was discharged on October 10, in good condition, with a diagnosis of psychoneurosis, anxiety state.

The patient has since been under observation at the psychiatric clinic of the Jefferson Medical College Hospital; until the week in which this report was made both the patient and his wife reported marked improvement over his previous state, with ability to work and make social adjustment which was in marked contrast to his previous condition. However, at the time of this report the wife stated that there had been some return of the previous symptoms. The patient was more restless and again complained of pain in the head, although it was still less severe than before. He offered few complaints but, on being questioned, admitted that he had not been quite as well. A psychometric examination on November 11 revealed a mental age of 8 years and 9 months, and an intelligence quotient of 55, which placed him at the level of a low grade moron.

This case is presented for the purpose of stimulating discussion with reference to the use of metrazol or other forms of shock therapy in the treatment for borderline mental conditions. There seems to be little doubt that the results obtained in this case were due largely to the psychotherapeutic implications of this drastic treatment. Yet can one say that psychotherapy was solely responsible for the beneficial change noted? May it not be that improved cerebral circulation played a part? If, however, one considers the treatment as largely psychotherapeutic, is one justified in utilizing such a dangerous method in treating patients, as in the case reported, or could one obtain the same results with less drastic therapy? On the other hand, one sees a fair number of patients, often of meager intellect, for whom the diagnosis rests between severe psychoneurosis and early schizophrenia. The results obtained with these patients by the use of ordinary psychotherapeutic measures have been notably poor; one sees them drift along for

years, economically dependent, socially maladjusted and personally uncomfortable and unhappy. Should one not make every effort to stimulate or shock such persons into a better state of mind?

PRELIMINARY REPORT ON METRAZOL THERAPY FOR THE PSYCHOSES. DRS. ROBERT S. BOOKHAMMER and EARL J. SAXE, Norristown, Pa.

The study includes observations in cases of schizophrenia and of marked depression with schizoid features. Careful clinical and laboratory examinations were made. Of 30 patients who received treatment 53 per cent showed improvement. Of these, 3 had remissions; 6 showed moderate improvement, and 7, slight improvement. No change was noted in 11 patients, and the condition of 3 became worse. The duration of illness for those who improved was less than two years. In many instances treatment was continued, with the hope of securing better results.

It was concluded that vastly more experience is needed before the role to be played by convulsive therapy in the treatment for schizophrenia can be properly determined. In all types of shock treatment there may be something significant which remains hidden, but which, if found, may furnish the key to the complex problem of the schizophrenic reaction. It is for this key that a search should be made while one is treating patients; one should not rest content with present formulations as representing the ultimate in specific therapy.

DISCUSSION

DR. KENNETH M. CORRIN: Dr. Bookhammer and Dr. Saxe asked me to discuss this paper from the point of view of convulsions as observed in laboratory animals—rabbits, cats and dogs. I am especially interested in the physiologic angle. The convulsant used has been monobromated camphor in olive oil, injected intraperitoneally. Seven and one-half grains per pound (0.5 Gm. per 0.5 Kg.) of body weight provides a severe grand mal convulsion. One first notices restlessness. There appears to be marked stimulation of the circulation. The cardiac sounds are loud and forceful. From ten to fifteen minutes are required before the convulsion develops. A few minutes before the convulsion proper definite changes are noted. The rabbits' ears become hyperemic. The cerebral cortex, observed through a trephine opening, takes on a pinkish hue. Small arterioles stand out prominently. Small vessels not previously seen come into view. The brain substance begins to force its way out through the trephine opening. When laminectomy is performed directly below the foramen magnum, similar hyperemic changes are seen to take place over the brain stem, suggesting a great increase in circulation.

With the onset of the convulsion contraction of the extensor muscles usually overcomes that of the flexors. The animal is frequently thrown backward. The chest is drumlike. Auscultation of the heart or palpation of the pulse is unsatisfactory. One hears nothing but the strong somatic muscular contractions. If one places the animal under the fluoroscope, the lungs are seen to be strongly expanded. The diaphragm is tense. Simultaneously with arrest in respiration, the heart comes to a complete stop, apparently in systole. This cardiac arrest can be verified by thoracotomy, artificial respiration being carried on by intratracheal insufflation. The brain herniates through the trephine opening and becomes vivid blue. The medulla oblongata, observed through a laminectomy opening, is forced down strongly into the foramen. The brain stem fills the entire foramen magnum, apparently blocking this area as an outlet for intracranial cerebrospinal fluid. A few minutes before the convulsion the blood pressure rises from the normal of 100 or 110 mm. to 130 or 140 mm. of mercury. During the acme of the convulsion the blood pressure rapidly rises to from 285 to 300 mm. This great vascular pressure produces great intracranial pressure. I was interested in Dr. Saxe's remark about not being able to hear the heart or feel the pulse in some cases. In from about 10 to 15 per cent of cases in which I have made examination during convulsions induced with metrazol there was cardiac arrest,

followed by bradycardia and arrhythmia. This cardiac irregularity, following the tonic phase in animals, is brought out distinctly with the electrocardiogram. The graph suggests heart block, with a rate averaging from 10 to 12 beats per minute. The bradycardia is quickly overcome, so that in about sixty seconds after the end of the tonic phase the heart has regained its regular rate. Arrhythmia may be more prolonged in some cases. A striking symptom is the pulmonary edema which develops rapidly with the tonic phase. Postmortem examination of animals shows marked edema and congestion of the lungs, brain and organs in general. With laboratory animals, one can use much larger doses of the convulsant to bring out prominently signs and symptoms for study. The convulsions I have described in animals are much more severe than those produced by metrazol therapeutically.

DR. HERBERT FREED: Drs. Bookhammer and Saxe should be congratulated on this well written paper concerning a timely topic. I believe that they have come to a just conclusion and that more time is needed to evaluate properly the results of this treatment. My colleagues and I have carried on the treatment for the same length of time that it has been used in the Norristown State Hospital. In that period, approximately two and a half months, we have seen remarkable changes in patients undergoing the treatment. However, a prominent displeasing feature has been the tendency to relapse, both during and, at times, after the course of treatment. While our period of observation is too short to justify a comparison of metrazol convulsive treatment and insulin shock treatment, it is my belief that the results of insulin shock are more profound and lasting, though possibly not as spectacular in the rapidity with which changes may occur. It is my personal conviction that changes in the fundamental personality of the patient can be produced with insulin. I have not seen such changes, as yet, with metrazol.

It is interesting to note that Angyal, in his series of 45 patients treated with metrazol, reported that 5 failed to react to metrazol but did respond to insulin. Angyal suggested that each drug may have its particular indications, e. g., insulin for paranoid patients and metrazol for stuporous patients. Perhaps a combination of therapies will be the treatment of the future, or possibly metrazol therapy followed by a course of insulin shocks if the patient does not respond to metrazol. While metrazol is easier to administer from the point of view of conservation of the time of nurses and physicians and the danger to life is probably less than with the use of insulin, the dislocations and, in some cases, the combined fractures are unpleasant. We have been fortunate to date in not having had such a complication. However, we have probably had the undesirable experience of accelerating the disease process in a case of undiagnosed fibroid pulmonary tuberculosis.

DR. A. P. NOYES, Norristown, Pa.: I recognize that nothing is yet known about the action of insulin or of metrazol; I wonder, however, if there may not be a common factor in the production of the beneficial results that follow their use. It occurs to me that this factor, if there is one, may be related to the unknown factor which is involved in the cases of schizophrenia in which violent trauma is followed by improvement. It has, of course, long been observed that a patient suffering from schizophrenia may show great improvement after a shock incident to severe trauma. Unfortunately, or perhaps fortunately, at the Norristown State Hospital my colleagues and I have had 2 instances of that type in recent months. One of Dr. Bookhammer's patients escaped from the hospital, stole a truck and, not being able to operate an automobile, ran it into a telephone post. The patient's skull was fractured, and he was so seriously injured that we believed he would die. Strangely, he lived and soon began to improve mentally. The outcome, from a mental standpoint, was fully as good as any attained with insulin or metrazol. Another patient was violently attacked by a ward mate, sustained a fractured jaw and was otherwise seriously beaten. He, too, began to show improvement after the injuries. It is interesting to speculate on whether in these three methods, insulin shock, metrazol convulsions and serious physical trauma, there may not be a common factor—one either of undetermined physiologic nature or in the form of a serious threat to the existence of the organism.

DR. F. H. ALLEN: Psychiatry has taken an interesting trend through the widespread development of these drastic methods of treatment. Both metrazol and insulin treatment constitute, as Dr. Noyes indicated, a form of shock therapy; they may represent a real death threat. In speculating on the reasons for improvement, one may find that the good results have a relation to this fact. The schizophrenic process is an attempt to achieve psychologic death through withdrawal into an unreal world. There then is a real threat, which may be a way of breaking into the schizophrenic condition.

In speculating on this I am reminded of an analogy in horticulture. It has been known that many wisteria plants that have never flowered can be brought to florescence by cutting the master root. This threatens the life of the plant, and the flower is a response. This is only an interesting analogy. The reactions in human beings, however, occur in association with a real death threat, and the results probably have some relation to this.

DR. HERBERT FREED: The question of the death threat has arisen frequently. I think that this is not the underlying factor in the response to treatment, for the following reasons: In my work with patients who have received only small doses of insulin, when it seemed that there could be no threat to the organism, either physiologically or psychologically, I have seen remarkable changes. For example, I recall a patient who was given a number of tests prior to treatment, injections of various types, which did not bring about any change in mental status. However, after the patient was given only two doses of insulin, 15 and 20 units, respectively, there was complete reversal of the mental status, with return to the normal. The only explanation the patient could give was that he felt better, with improvement in appetite. Deutsch (The Mentally Ill in America: A History of Their Care and Treatment from Colonial Times, New York, Doubleday, Doran & Company, 1937) reported that the treatment for mental disease from 1780 to 1820 consisted of various technics for "frightening the patient out of his psychosis," e. g., letting him fall through a trap door into a well of cold water, chaining him in a well and allowing the water to rise till he practically drowned or throwing him into a dungeon filled with snakes and vipers. This was the era when the outlook for mental disease was considered hopeless.

DR. R. S. BOOKHAMMER: In answer to the question about the types of schizophrenic patients who have improved after treatment with metrazol: It may be said that good remissions have been obtained in those who had predominant paranoid reactions as well as in those who had been catatonic and stuporous. Good results have also been obtained in 3 cases of severe depression associated with schizoid features. We are now treating patients who have had insulin therapy without improvement. It is too early to report any results for this group.

With regard to spilling the drug outside the vein: I am not particularly concerned. It has happened in several instances, and there was no local after-effect. The drug was quickly absorbed.

I have noted a tendency toward relapse after treatment was discontinued. One patient, who had been ill for over a year, showed splendid improvement, and her release from the hospital was being considered. Two weeks after treatment was discontinued she returned to her former state of mutism and negativism.

It is not likely that insulin or metrazol therapy, or a combination of both, will be the treatment of the future. It is likely that something else eventually will take their place. As Dr. Noyes has pointed out, trauma, insulin shock and convulsions produced by metrazol all seem to have something in common. We are not sure what it is that produces the results that we have obtained. While we acknowledge that our treatment is empirical, the important thing is that we secure results. It should be emphasized that the use of metrazol is not a cure for dementia praecox. There seems to be justification for considering its use as an aid in securing improvement.

A Study of Involutional Melancholia. Drs. Harold D. Palmer and Stephen H. Sherman.

This paper will be published in a later issue of the Archives.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Moses Kerschner, M.D., *President of the New York Neurological Society, in the Chair*

Joint Meeting, Nov. 16, 1937

Mental Changes in Chorea Minor. Dr. Donald Shaskan (by invitation).

Thirty-five cases of chorea minor associated with varying degrees of mental change are presented. Group 1 consisted of 16 cases in which there was no gross mental change. The patients were from 7 to 15 years of age. They showed marked emotional instability, which is characteristic of the disease. There were no significant facts concerning the behavior or personality of the children or family history.

In group 2 were cases of chorea associated with mild mental disturbances; the patients ranged from 8 to 21 years of age, with only 2 older than 13. One death occurred in this group. Behavior difficulties were manifest and of such magnitude that psychiatric treatment was called for. The children were aggressive, had temper tantrums and suffered from delusions of ridicule. Disappearance of behavior problems did not occur simultaneously with subsidence of the choreic attacks. However, as a rule, alleviation of mental symptoms was closely associated with physical improvement. Fever therapy was beneficial in this group.

In the 8 cases of chorea with associated psychosis and severe carditis in group 3, the more serious nature of the prognosis was aggravated by the severity of the psychosis. The mortality rate was 50 per cent. Fever therapy did not prove beneficial in this group. In 2 instances the prognosis was poor, even if the choreic process was disregarded.

The mental changes associated with chorea minor are closely connected with disturbances in emotional impulses. Emotional instability and increased laughing and crying predominate. Hyperkinesis and akinesis influence "the stream of thought." Hallucinations and delusions appear, and in the most severe forms confusion and disorientation may supervene.

In severe states, when hyperkinesis overshadows the other phenomena, as well as when hallucinations and delusions occur with clear consciousness, one may be struck by a symptomatic similarity to schizophrenia, but the resemblance is superficial. The fundamental character of chorea is emotional instability, not the regression and withdrawal of schizophrenia. The person with chorea is overwhelmed by an autonomous brain function which interferes with his relation to the world—a relation which he would like to maintain but is forced to forego. The schizophrenic patient, on the other hand, has primarily a tendency to give up his relation to the world. Obviously, some of the mechanisms active in both schizophrenia and chorea with psychosis are the same.

DISCUSSION

Dr. Karl M. Bowman: Dr. Shaskan has given what is essentially a series of case reports of chorea minor and has grouped them under three headings depending on the severity of mental symptoms. He has emphasized the organic nature of the disorder and the organic features of the mental picture. He has pointed

out that there is some resemblance to schizophrenia, but if one studies his case records there is in most instances little chance of confusing the mental picture of chorea minor with that of schizophrenia. As he pointed out, in chorea there is usually insight; the patient realizes that he is sick, and the picture is that of an organic type of mental disorder, as opposed to the characteristic picture of schizophrenia.

Dr. Shaskan reports that fever therapy is of benefit in mild forms, but is of little or no benefit in severe states. It is not entirely clear to me how he determines this. Four of the patients with severe disease improved, and 4 died, so that the mortality rate is 50 per cent. Of the 4 patients who died, 3 were given fever therapy. I suppose, therefore, that one must rely on the clinical observation of the physician who is treating the patient as to the value of fever therapy for this disease. However, when one is told that another author reported a similar series of cases in which the mortality rate was 80 per cent, one may inquire whether the mortality rate would not have been higher in Dr. Shaskan's series if fever therapy had been omitted. It is also worth noting that the type of fever therapy used in all but 1 case was injection of triple typhoid vaccine. One might ask whether the use of other types of fever therapy might not be of benefit and whether Dr. Shaskan can give figures or observations to show the value of other types of fever therapy in severe forms of chorea. As to whether fever therapy is of value in the very mild forms, it is again possible to quibble. One would expect that patients with this type of the disease would recover without fever therapy; I ask Dr. Shaskan to say exactly how he determined that fever therapy is of value when the disease is mild but of little or no value when it is severe.

Dr. S. Bernard Wortis: Chorea is only a symptom of disease or dysfunction of the brain; the etiology of chorea is, of course, varied. Rheumatic infection may cause in one person swollen joints, lesions of the skin or subcutaneous nodules; in another, carditis; in a third, patches of swollen or injured brain (encephalitis) resulting in involuntary, incoordinated movements, which may be sufficient to incapacitate him or so mild as to give him only mental anguish, and in a fourth, mild mental disturbance or severe psychosis. Furthermore, the mental disturbance will depend on the individual patient's experiences, which will color the content of the psychotic productions. All these data indicate only how little is yet known of the variations of constitution. There are needed studies on the correlation of mental signs and symptoms and the previous personality structure of persons with chorea.

In the data shown by Dr. Shaskan, it is pertinent that 3 of the 4 patients with severe disease who died had no evidence of carditis. Marked mental symptoms in somatic disease are a grave prognostic omen.

It is important to stress that in children with mild chorea behavior problems and feelings of inferiority with overcompensation may occur, owing to concern over the mild, uncontrollable, rheumatic choreiform reactions. The children are suddenly projected into uncontrollable foreign behavior and may have difficulty in adjusting to it.

Dr. Shaskan has given the severer side of the picture, in which the mental disturbances are based primarily on moderate and severe dysfunction of the brain. In cases of the severe type he has shown the effect of pronounced structural (encephalitic) or circulatory defect on brain function. He has demonstrated that there are combinations of the so-called organic syndrome (i. e., behavior reaction deficit) and the delirious hallucinatory reaction type—the former characteristically producing defect in memory, judgment, sensibilities and emotional control and the latter giving a picture of bewilderment, disorientation, vivid hallucinations and delusions, in an emotional setting of fear.

The mental signs and symptoms of chorea are often overlooked, because one tends to relate the symptoms of chorea to the pure motor disturbances and thereby to overlook a great deal of the mental and emotional picture.

Dr. David I. Arbuse: I wish to inquire as to the dose of typhoid vaccine used in these cases and the highest fever reaction to any given dose, as marked

hyperpyrexia and death have been known to occur soon after a relatively small dose was administered intravenously. In cases of chorea with psychotic manifestations it is likely that other factors besides the therapy may account for a fatality.

DR. ISRAEL S. WECHSLER: It is a pity that Dr. Shaskan has not presented some pathologic material as a basis for his statements. His clinical descriptions are familiar. Chorea is not often accompanied by mental symptoms, and one sees true psychotic symptoms comparatively rarely. It seems to me that what he has described are cases of encephalitis. The pictures are typical of encephalitis, with the various involuntary movements, of which chorea is only a manifestation. It is erroneous to regard chorea as a disease; it is a symptom which occurs on the basis of various pathologic conditions. In certain cases the chorea so dominates the picture that one calls it a disease, such as that of Sydenham or of Huntington. The combination of chorea and delirium and other mental symptoms, which Dr. Shaskan described, as well as that of chorea, tremors, changes in tonus and other involuntary movements, is typical of encephalitis. Such encephalitis may be of the epidemic variety, or may have as a basis some other pathologic lesion. French and other writers described the pathologic changes of chorea as due to minute emboli from valvular disease. If Dr. Shaskan had been able to present pathologic material, he would have enabled one to determine whether he had described "simple chorea" or some form of encephalitis with choreic and other manifestations.

DR. DONALD SHASKAN: In reply to Dr. Bowman's question about the use of fever therapy: Dr. Sutton and her co-workers (Sutton, L., and Dodge, K.: *J. Pediat.* **3**:813, 1933) showed the value of fever therapy in cases of chorea in which there were no gross mental changes, the type of disease usually found in the pediatric ward, and I believe that I can corroborate her findings in cases of chorea associated with mild mental disturbance. I cannot say definitely that fever therapy is beneficial in the severe forms, in view of the high mortality rate. It may be, or it may not.

The dose used in fever therapy is best described in Dr. Sutton's original articles. She started with a dose of 0.05 cc. of triple typhoid vaccine and increased it as long as she could get a fever response. I think she considered a fever response to be any temperature above 104.

In reply to Dr. Wechsler's remarks: I have one pathologic specimen, which was examined by Dr. Lewis Stevenson. He did not observe any unusual changes. He could say neither that the lesions were encephalitic nor that the chorea had changed the brain in a typical fashion.

CEREBRAL LESIONS DUE TO VASOMOTOR DISTURBANCES FOLLOWING TRAUMA TO THE BRAIN. DR. MAX HELFAND (by invitation).

DISCUSSION

DR. CHARLES DAVISON: The problem of pathologic changes due to vasomotor disturbances following trauma to the brain, as stated by Dr. Helfand, is difficult to solve, especially in the absence of objective neurologic signs and symptoms immediately following the trauma. The appearance of neurologic or psychiatric symptoms years after onset of the trauma makes the problem even more difficult, as frequently it is almost impossible to determine whether the so-called post-traumatic symptoms may not be the result of a new disease of the nervous system, independent of the trauma.

Most of the patients reported by Dr. Helfand died a few hours or days after the trauma. His recapitulation of the pathologic changes in the nervous system in such instances is of interest. Patients 14 and 22 apparently lived many years after the injury. Patient 14 had an old war injury in the left ear which rendered him unfit to continue his occupation as an automobile instructor. In this case there was a crater-like defect in the cortex. I should like to know how long this patient lived after the injury and what neurologic signs and symptoms were found.

Patient 22, who suffered from cardiac disease, had a history of injury to the brain following an automobile accident. In this case there were lesions in the frontal lobe, Sommer's sector, the cerebellum and the putamen. Here, again, I wish to know how long the patient lived after the injury and whether any mental or neurologic symptoms were present in the period following the injury to the brain.

Recently, I had opportunity to study the brain of a patient who had received an injury to the head and who complained of headache for a number of years afterward; there were no neurologic signs or symptoms. The case became a medicolegal problem, and the patient was considered to have a motivated psychoneurosis; compensation was not allowed. Several years later he committed suicide by hanging; at autopsy old traumatic lesions were observed in the right orbital and temporal convolutions. Cases like this offer the greatest problems, and some agreement must be reached concerning them. When is a patient malingering, and when is he truly entitled to compensation for trauma and inability to make a complete return to his occupation?

The cases reported by Dr. Helfand, except cases 14 and 22, do not help much in the understanding of this problem, except from the purely pathologic angle.

The terms "softening," "anemic necrosis" and "infarct" are, in my opinion, stages in the encephalopathic process following trauma or other causes, such as atherosclerosis or toxic processes. These descriptive terms can be used as one wishes so long as it is remembered that they represent stages of a traumatic encephalopathic process. I agree with Dr. Helfand in his classic description of the histopathologic changes following immediately or shortly the closure of a vessel (anemic softening) and temporary vascular occlusion (anemic paling). I wish to ask Dr. Helfand: How frequently has he observed involvement of the cornu ammonis and the cerebellum in his cases? Were most of the pathologic changes in the brain seen in the region subjected to the blow? How frequent were lacerations of the brain? I also agree with Dr. Helfand that the small distal hemorrhages, as described by Spielmeyer, are due to functional disturbance of the vessel through vasomotor influence. With reference to the absence of rupture of walls of vessels in so-called red softening, I cannot fully agree with Dr. Helfand or Dr. P. Schwartz. In some of my studies on injury, I found evidence of rupture of vascular walls in the hemorrhagic areas and in the areas of "red softening."

The vulnerability of the cornu ammonis, as pointed out, is additional proof for the theory of vasomotor disturbances following brain trauma.

Dr. Armando Ferraro: In discussing Dr. Helfand's paper, one must accept the facts which he has presented at their face value. He has furnished photographic documentation of areas of necrosis and of hemorrhagic softening following traumatic lesions. From the material studied he has reached the conclusion, which favors the conception already expressed by other authors, that the pathologic changes following brain trauma have a functional origin, when one uses the term "functional" in the sense of the equivalent of vasomotor imbalance.

It is unfortunate that in such a short period it is possible neither for him to give the details of his histologic investigations nor for the discussers to take up the many important issues of his presentation. I shall therefore limit my discussion to a particular aspect of this important problem: that of pathogenesis of both the necrosis and the hemorrhagic softening. If one submits the ear of a rabbit to repeated traumatic stimuli one observes that there is an early stage of ischemia, followed by a period of reddening of the ear during which even a few small hemorrhages are noticeable. The condition of the blood vessels in the second stage has been called stasis or prestasis by Ricker. Prestasis is the result of vasovagal reflexes which produce dilatation of the blood vessels involved. In the process of prestasis or stasis there are slowing down of the blood current and a tendency toward diapedesis of red blood cells. As a result of slowing down of the blood stream, nutritional changes take place in the surrounding tissues, and a more or less advanced process of necrosis may follow. In prestasis, therefore, two conditions occur: (1) the reaction of the tissue to impaired nutrition and (2) the output

of red and, eventually, of white blood cells. These conditions have a certain independence, so that at times a severe process of necrosis may occur without diapedesis. At other times, diapedesis predominates.

One thus meets the first controversial point in the pathogenesis of traumatic necrosis, as represented by vasospasm versus vasodilatation. Vasospasm naturally leads, according to its severity, to a more or less advanced process of necrosis, up to complete white softening. However, so does the stasis or prestasis of Ricker. What, therefore, is the mechanism by which the lesions following traumatic injury are produced? In this respect, I believe that, except for experimental work, histopathologic study is of little assistance, first, because of the time element which elapses between trauma and postmortem examination and, second, because agonal and postmortem influences may change the lumen of the blood vessels. Another point to be taken into consideration is the possibility that during vasospasm, if this takes place, certain metabolic products may result from anoxemia—products such as acetylcholine, adenosin and histamine, which produce vasodilatation and might, therefore, cause disappearance of the original spasm.

Comparison with other pathologic conditions may result in clarification. In some of my studies on arteriosclerotic softening, in which the mechanism of vasospasm has frequently been invoked, I have found that certain blood vessels appear to be contracted at a certain point in their course, whereas at other points, particularly beyond the contraction, vasodilatation is evident.

I am therefore under the impression that angiospasm and angiodilatation are intimately correlated processes, and it may well be that an original angiospasm, even though of short duration, might ultimately produce vasodilatation, with all the characteristics of stasis and prestasis as advocated by Ricker. I am therefore inclined to accept the idea of a mixed type of pathogenetic mechanism in the production of traumatic lesions—an interplay of vasospasm and stasis, both leading to anoxemia—rather than either of the conceptions alone.

In the matter of massive hemorrhage and hemorrhagic softening which are so frequent in traumatic lesions, the pathogenesis is still a complicated problem. I believe that massive hemorrhage, when present, may be the result of tearing of a blood vessel—hemorrhage by rhexis. Whenever punctiform hemorrhages dominate the picture, the mechanism of stasis and prestasis as advocated by Ricker, with diapedesis of red cells, is the most probable. One cannot easily conceive of a large pool of blood as a result of diapedesis, whereas the minute hemorrhages in which nerve tissue is intermingled with red cells might well represent a process of diapedesis.

In a traumatic lesion diapedesis does not necessarily require the preexistence of pathologic changes in the walls of blood vessels, such as those described in other conditions under the term "angionecrosis," which lead to spontaneous hemorrhages. Under the influence of trauma, the vasomotor imbalance resulting from the vibration might be sufficient to produce a transitory state of stasis or prestasis in which diapedesis takes place. Therefore I agree with Dr. Helfand in thinking that angionecrosis in traumatic conditions may be secondary, and not primary. If, for any reason, a process of angionecrosis is present at the moment of trauma it will necessarily favor more diffuse and intense damage, since a larger number of blood vessels may be predisposed to bleeding.

This brings me to the practical point of evaluation of the effects of trauma to the head in relation to the age of the patient and possible preexisting medical conditions. As age, through arteriosclerosis, cardiovascular disease and particularly renal disease, may predispose to angionecrosis—a preparatory step toward hemorrhage—it is only fair that in evaluating the effect of a trauma of the head one should take into consideration the age and general medical aspect of the patient and consider the possibility of definite organic changes as the basis of some of the posttraumatic symptoms.

Finally, to explain the progressive course of posttraumatic symptomatology, one may take into consideration the fact that after the initial hemorrhage or hemor-

rhagic softening metabolic changes result from the disintegrated nerve tissue and that metabolic products may, in turn, be responsible for a more or less definite process of necrosis of the surrounding vessels and establish, therefore, a condition of stasis and prestasis as a result of which additional diapedesis may take place at the periphery.

DR. LEWIS D. STEVENSON: I find it difficult to distinguish between a traumatic and a vascular lesion in the brain. The criteria are not absolute. It is strange that vasospasm is seen more often in epilepsy than in any other condition. In some of the moving pictures which Dr. Penfield has made at the operating table one sees a periodic contraction of the blood vessels in the pia. This lasts several seconds, or perhaps longer; yet, as far as I can say, there are little disappearance of tissue and few lesions like those described tonight. It is assumed that in trauma there is constriction of the vessels. This is not really known. In epilepsy there are vasoconstriction and little disappearance of tissue. In my opinion, with trauma to the brain there is nearly always hemorrhage, and hemorrhage, more than anything I know, promotes activity on the part of the microglia. I think the microglia cells eat up the brain and are largely responsible for the lesions reported tonight and for the disappearance of tissue which one can demonstrate by encephalogram. I have seen lesions in the brains of alcoholic, arteriosclerotic and epileptic persons similar to many shown here on the screen; I do not think that they can all be attributed to trauma.

DR. FOSTER KENNEDY: There came to my mind about half a dozen men whom I saw in the World War who had been wounded by a machine-gun bullet across the spine. After they had sustained a "gutter" wound across the back they had for varying periods—from fifty-six hours to two weeks—a picture of pure spinal tabes, with considerable sensory changes and loss of deep reflexes, sphincter control and vibration and position sense, without loss of motion in the legs. They temporarily had lost function in the posterior spinal columns—a condition which apparently had been produced at a distance from the impact, as in the cases reported here. The condition I have described is associated with considerable trauma, such as a bullet wound. One neglects, I think, the effects of severe mechanical vibration in producing temporary dysfunction in nerve tissue, which Dr. Helfand has called "functional." I prefer to use a word which some one has suggested—"reversible"—referring to a symptomatology which is capable of alteration and return to the normal. The condition I have described is unequivocal; it is the result simply of what may be called localized commotion of the nearest part of the spinal cord—a condition which might, if it had been subjected to pathologic investigation in the cases mentioned, have presented a picture similar to that in Dr. Helfand's cases.

DR. RICHARD BRICKNER: I wish to raise another point in connection with concussion of the spine. Occasionally one sees a case in which there has been severe jarring with some general shock, and it is not until after a number of hours, or even a day, that evidence appears of actual focal lesions in the spinal cord. One usually says that these lesions are due to edema which has been slow in development—a conception which is not altogether satisfactory. It is equally difficult to explain the situation on the basis of hemorrhage or thrombosis, because of the long interval between the injury and the appearance of the symptoms. I wonder whether the phenomenon Dr. Helfand has discussed might help to explain this phenomenon.

DR. MAX HELFAND: I wish to thank Dr. Ferraro for his enlightening discussion. Of course I could not get everything into twenty minutes' presentation, since the material was so large and the changes were so extensive, but I wish to assure Dr. Ferraro that I, as well as my teachers and friends who helped me, also think that not only angiospasm but angiospasm and stasis are involved.

Dr. Stevenson remarked that the lesions are not attributable only to trauma. Of course not. I do not think they are specific to trauma, for they are observed

in association with epilepsy, tuberculous meningitis, carbon monoxide poisoning, air embolism and arteriosclerosis, but at all times they are due to functional disturbances of the vascular apparatus.

Dr. Kennedy's term "reversible" is a good one from the clinical standpoint; let me stress, however, that I did not say anything about the clinical picture in this paper. This was only a histopathologic demonstration of lesions that are attributable to changes with trauma. I hope at some time in the future to report on the clinical considerations, but may I suggest this point? I believe that these lesions do not produce specific neurologic signs which point to a localizable lesion —a point which arises in connection with Dr. Davison's discussion. I believe that a person with neurologic signs presents not only signs of a lesion but signs of a whole personality associated with a lesion.

Dr. Davison asked how frequently traumatic lesions occur in the cornu ammonis and the cerebellum and whether other diseases produced the signs in the cases reported. These 22 cases were taken from a large group, but I purposely eliminated any case in which there were signs of arteriosclerosis, epilepsy or other disease, so that the lesions in these cases must be attributed only to trauma. There was no other disease, and the patients lived only from one to six days after the injury, during which time no other disease occurred. That is why I was careful to limit the presentation to 22 cases.

I agree with Dr. Brickner that some of the "fleeting" signs are due to "fleeting" vasomotor disturbances, and they are, as Dr. Kennedy said, reversible.

OXYCEPHALY: A NEW OPERATION; RESULT (A PRELIMINARY REPORT). DR. JOSEPH E. J. KING.

Oxycephaly is believed to be due to premature closure of the cranial sutures. If nothing is done to relieve the condition it is likely to result in atrophy of the optic nerve, owing to prolonged and marked increase in intracranial pressure. Blindness and, in extreme cases of exophthalmos, loss of the eyeballs finally result.

Operations which have been advised for this condition include: subtemporal decompression, unilateral or bilateral; linear resection (Lannelongue and Lane); resection of the optic canals (Elschnig): linear craniectomy (Faber) and circular resection of the skull (Bauer), or a combination of these procedures. It is believed that none of these operations will permit symmetrical expansion and normal growth of the skull and brain, although temporary relief of the exophthalmos and defective vision may result.

A new operation in two stages, as performed on a boy aged 8, is described. A flap consisting of scalp, galea, temporal fascia and muscle and the pericranium was turned down. The flap was horseshoe shaped and attached in the temporal region and included almost all one side of the head. Burr holes were made about the periphery of the exposed skull, about 2 inches (5.08 cm.) apart, and several other burr holes were made in the central part of the exposed skull. With a de Vilbiss forceps channels were cut connecting the holes, and the bones of the cranial vault were cut into triangular and rectangular shapes, creating a "mosaic." The fragments of bone varied in size from 1¾ to 2 inches (4.5 to 5.08 cm.) on one side. Bleeding from the scalp flap was controlled by the use of a pedicle clamp and skin clips. The dura was not opened. It was thin, transparent and redundant. The fragments of bone separated widely, one from another. The scalp flap was returned to its position over the morsellated skull fragments and sutured in two layers, without drainage. A copious dressing was applied and covered with a plaster shell.

On completion of the first stage of the operation it was observed that the head on the side of operation had a round contour, as compared with the rooflike appearance of the other side. The exophthalmos on the side of operation had receded to a marked degree—in fact, had almost disappeared—and that on the opposite side had greatly diminished.

The boy made an uneventful recovery. Six weeks later the other side was operated on in the same manner. Vision, which had been poor, was markedly improved. The head had a normal round contour. The fragments of bone on both sides of the cranial vault were firmly united. The boy's apathetic appearance had changed to one of alertness.

This is a preliminary report. It is hoped that a later and favorable report can be made.

DISCUSSION

DR. FOSTER KENNEDY: I do not know what I, as a mere physician, can say about this. It has not been discovered why people have oxycephaly. It may be that there is something wrong with the parathyroid and calcium metabolism. What the surgeon has done in this case is to neglect prime causes and go to work. He has exhibited his result, so that my discussion becomes a description of what I think he has done. It is not an elucidation, for I cannot elucidate what has been particularly illuminated. His motto ought to be *fortiter in arduis.* A brief remark he made should be noted: In order to perform the operation at all it was necessary, of course, to control hemorrhage. In order to control hemorrhage it was necessary to invent an instrument with which to do it, and simply in passing, in a mere sentence, he said: "Here is a pedicle clamp"; he did not say it even as emphatically as that. It perhaps was not noticed that he invented the pedicle clamp with which to control the hemorrhage from the scalp in this extraordinary operation. This is a piece of consummate surgery; it is a work of art. All artists are persons who make a pattern out of inchoate material, so that people who are unable to see such a pattern understand the inchoate through them.

DR. S. BERNARD WORTIS: I also wish to add a word of praise for Dr. King's courage and skill in performing this new operation. He has reopened bone sutures, where nature prematurely closed them, and has accomplished as physiologic an operation for oxycephaly as one could conceive. Incidentally, he has demonstrated several other important points. With release of the increased intracranial pressure there was regression of the proptosis. I am reminded of a case which Dr. Dan Renner described at the meeting of the American Psychiatric Association this year—that of a blind boy with oxycephaly who had had no relief from subtemporal decompression. Every time he tried to close his eyes they popped out of his head, so that eventually infection of the eyes with corneal and conjunctival sloughing resulted and bilateral enucleation was necessary. Dr. King saved his patient's sight and insured the normal growth of the brain by permitting an increase in the intracranial cavity.

Another interesting point is that production of convolutional markings in the skull, due to increased intracranial pressure, is a reversible phenomenon. When the intensely severe intracranial pressure was relieved, normal surface contour returned to the inner table of the skull, as demonstrated in the roentgenograms.

TREATMENT OF ACUTE AND CHRONIC SUBDURAL HEMATOMA. DR. ABRAHAM KAPLAN.

The subject of subdural hematoma has aroused increasing interest during the past decade because of the many cases of indirect injury to the head in accidents due to speeding.

There is need for a clearer differentiation of the acute and the chronic phase of subdural hematoma. Whereas operative intervention for chronic subdural hematoma is practically always necessary, this is not true of the acute form. A hasty operation in such a case can only end disastrously. The injured person with a small margin of safety, who might well be saved by medical measures, such as treatment for shock, dehydration, avoidance of undue manipulation and judicious lumbar punctures, may easily have his chances jeopardized by the additional trauma of an operation.

There are reviewed only 4 instances of acute subdural hematoma in which operation was performed. One patient recovered, with residual paresis and hemianopia. In the other 3 cases postmortem examination showed lesions which were beyond surgical aid. Many similar instances could be cited.

Fourteen cases of chronic subdural hematoma are presented in which operation was carried out. In 2 patients the lesion was bilateral. Only 1 fatality occurred and that was ten days after operation, from a pulmonary embolus. The operative site showed no recurrent bleeding or cerebral edema.

Is chronic subdural hematoma merely an advanced stage of the acute form, or is it a distinct entity? The differential points are given in the accompanying tabulation:

	Acute Subdural Hematoma	Chronic Subdural Hematoma
Type of trauma.....	Severe, often followed by unconsciousness	Slight and may be forgotten; direction of blow in antero-posterior diameter; rarely loss of consciousness
Fracture of skull....	Frequent	Almost never
Source of bleeding...	Arterial as well as venous; laceration of brain	Only venous bleeding; no laceration of brain
Symptomatology....	Almost immediate onset of symptoms	Characteristic latent interval from days to months
	Seldom any fluctuation of consciousness	Periods of fluctuation in consciousness
Clinical findings.....	Early coma, which persists, and patient dies, or diminishes and patient may recover	Coma a late manifestation
	Paresis; signs of pyramidal tract involvement on side opposite the lesion	Often paresis, signs of pyramidal tract involvement and dilated pupil on side of hematoma
	Convulsions not unusual	Convulsions conspicuously absent in entire series
	Aphasia associated with lesions in left hemisphere in right-handed persons	No aphasia in 9 cases of extensive hematoma over left hemisphere in right-handed persons
Spinal fluid.....	Uniformly bloody or pink	Xanthochromic; sometimes clear

Bilateral trephination over the postparietal region is advocated as the best site for localization and removal of the chronic subdural hematoma. Through the trephine opening irrigation in all directions is performed, with the aid of a catheter, until the return washings are clear and the brain has approached the dural surface. In cases in which hematoma is suspected but has not been located, ventriculograms can easily be made through the existing trephine openings, to aid in the diagnosis.

DISCUSSION

DR. FOSTER KENNEDY: In an earlier paper on this subject, Dr. Kaplan placed a good deal of emphasis in diagnosis on the sidedness of the lesion with respect to that of the dilated pupil; I notice in this larger series that the dilated pupil was on the side of the lesion in only 7 of 14 cases; I do not believe, therefore, that his earlier observation was entirely justified. Much more important is Dr. Kaplan's wise insistence not on the ease of diagnosis but on the importance of bilateral trephination, come what may in diagnosis. He has shown admirably at the Bellevue Hospital how important it is not to be too nice in diagnosis in these cases but to act at once; he also has given assurance that bilateral trephination in the posterior parietal area is associated with no more shock to the patient than is, for instance, transportation to the roentgenographic department. The diagnostic procedures that one goes through, the waiting for new signs, are all waste time, waste motion, and are dangerous; it is much better, if one suspects this condition, to perform a bilateral trephine operation immediately.

I am not sure whether Dr. Kaplan's insistence on the differentiation between acute and chronic subdural hematoma is entirely justified. I wish to ask him whether this is not a distinction without a difference—a matter of degree. If the hemorrhage is violent enough, associated of course with laceration of the brain, it may be classified as an acute subdural hematoma, curable by surgical means. If, on the other hand, the hemorrhage is small, occasional, repeated, interrupted and then renewed, the situation is similar to what Dr. Kaplan calls an acute subdural hematoma, but is one in which the clot is piled up. Here the clot is not usually associated with laceration of the brain and can be evacuated and the patient saved, but differentiation between the two seems to me one more of quantity than of quality.

There was an amusing incident in the wards two or three weeks ago, in which we of the attending staff deliberated with a good deal of doubt regarding the condition of a Chinese patient. He was not able to give any history, so that we were deprived of that information; nothing, however, was farther from our thoughts than the possibility of a subdural hematoma. I thought he had a tumor of the brain and asked that the surgeon make a ventriculogram. There was so much pressure that we thought this procedure was wise, and so it was, for when we made a head puncture we found a subdural hematoma. So one occasionally is right, almost by inadvertence.

Another minor point of which Dr. Kaplan did not speak: There are many instances of what might be called "medical" spontaneous subarachnoid hemorrhage. My colleagues and I are not sure to what it is due. We think that on the whole it is epidemic in nature, and I believe many physicians agree. The condition is easily diagnosed, and one can hardly be misled; lumbar puncture shows free blood in the spinal fluid. Yet cases of this kind were not seen till about ten years ago. A great many have been seen since. They occur in outbreaks, and in some instances the hemorrhage is associated with severe papilledema, with hemorrhages, and a tremendous rise in intracranial pressure. I think that pressure is due more often to block of the iter than to the clot, but it is possible there are cases in which there is clot formation. I believe one ought, in doubtful cases, to be prepared to do what Dr. Kaplan advises—at least a bilateral trephine operation, as well as lumbar puncture. A patient was brought to the hospital eight or nine years ago with a diagnosis of delayed apoplexy. I did not believe that it was "straight apoplexy" because all patients with delayed apoplexy whom I have seen died of ventricular hemorrhage and this man had had a very small bump on the head. He had had, after a minor accident, severe pain in the head. Eight days later, according to notes of the hospital, he became unconscious and aphasic, with right hemiplegia and papilledema; he had fever for six or eight weeks. He took action against the state of New York. I was asked to see him years afterward. I told the surgeon I did not think he had delayed apoplexy, and I was lucky enough to find a triangular nevus on the appropriate—the left—side of the head, which extended over the motor area, with the base exactly in the midline. The patient had had a minor injury and a minor hemorrhage, which had taken eight or nine days to attain such dimensions as to cause paralysis, headache, aphasia and papilledema. It is worth while to bring to attention the importance of investigation of the scalp for small nevi—not always small, for they are often large, but not pronounced. One has to look about in the hair for this condition, which appears always as a lake of blood or as friable vascular walls. The weakness has persisted through all the layers of the embryo, making possible this situation after a minor trauma.

I think Dr. Kaplan's elucidation of this subject during the last half-dozen years has been helpful.

DR. IRA COHEN: I am indebted to Dr. Kaplan for his careful analysis of the signs and symptoms in the cases he has described this evening, not only the signs that he mentioned as having been found with hematoma but those that he stressed as absent. I refer particularly to convulsions and aphasia. Fourteen cases

of hematoma is a large group, and that aphasia was absent in 9 cases of lesion on the left side is worthy of comment. When the question arises in diagnosis as to whether a lesion on the left side is due to a hematoma or a neoplasm, the fact that speech difficulty is found will throw the balance somewhat in favor of a tumor. I recall, eleven or twelve years ago, demonstrating at a meeting of this society a man with an allied condition, a subdural hydroma on the left side, who showed speech disturbances; it is possible, therefore, that in a larger series of cases of hematoma involving the left side speech difficulty might be found.

I have not seen convulsions associated with hematoma. I have had 2 patients with convulsions who acquired a hematoma as the result of a fall during a convulsion, but the convulsions were not due to the hematoma.

I take issue with both Dr. Kaplan and Dr. Kennedy that acute and chronic subdural hematoma are part of one process, or even that they should be discussed in one paper. Acute hematoma, so-called, is due to an acute hemorrhage, and nothing else, immediately following a severe injury to the head. As such it is part of the injury, as a depressed fracture might be, or any other complication which is the immediate result of the injury. On the other hand, a chronic subdural hematoma is, in my opinion, a rather slowly expanding lesion and one in which there is the history of a mild trauma. It offers frequently considerable difficulty in diagnosis and is sent to the surgeon somewhat as a compensation, when he finds it, for disappointments in other surgical conditions. I am sure the last word has not been said as to the development of hematomas. Dr. Kaplan referred to recurrent hemorrhage as an etiologic factor, disregarding the work of W. James Gardner (Traumatic Subdural Hemorrhage, with Particular Reference to the Latent Interval, ARCH. NEUROL. & PSYCHIAT. **27**:847 [April] 1932), who offered a different, but acceptable, theory.

The treatment outlined by Dr. Kaplan is the accepted method today. It is the simplest treatment and, from his figures, obviously gives the best results.

DR. ABRAHAM KAPLAN: I believe it is important to differentiate between acute and chronic subdural hematomas because, with the great increase in the number of injuries of the head, many patients with acute subdural hematoma will be subjected to unnecessary operation if no attempt is made to distinguish between the two conditions. Unless the differential points are carefully considered, many cases will be placed in the wrong group. I have often been happily surprised to see the results of conservative measures in cases in which the patient remained in coma for days, or even weeks, after an acute injury of the head and who finally recovered completely.

From an active service such as that at the Bellevue Hospital, my associates and I are able to report only a relatively small number of cases of chronic subdural hematoma. The reports from other clinics of more than 100 cases of subdural hematoma undoubtedly include many of the acute type. As Dr. Cohen has well pointed out, acute subdural hematoma is not an isolated finding but part and parcel of the picture of an acute, severe injury to the head, which invariably includes laceration of the brain and skull fracture. Operation on the patient who has sustained this type of injury, except in selected cases, only adds to his troubles and subtracts little from the existing insult.

Dr. Kennedy has referred to dilatation of the pupil on the side of the hematoma, which, if one bases judgment on the present series of cases of chronic subdural hematoma, is, I must admit, not as valuable a sign as I first thought. Nevertheless, if one disregards the 2 cases of bilateral chronic subdural hematoma, the sign was of diagnostic significance in 7 of the remaining 12 cases. It is not difficult to realize that previously bilateral craniotomy, or even unilateral craniotomy on the wrong side, was more than a comatose patient with subdural hematoma could tolerate. Now that most neurosurgeons prefer bilateral trephine exploration for the localization and removal of a chronic subdural hematoma, the value of the dilated pupil as a guide to the side of the lesion is not as great.

PHILADELPHIA NEUROLOGICAL SOCIETY

J. W. McCONNELL, M.D., *President, in the Chair*

Regular Meeting, Nov. 19, 1937

DIFFUSE POLYMORPHOUS NEUROFIBROMATOSIS, WITH UNUSUAL INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM. DR. ALFRED GORDON.

Recklinghausen's disease presents many variations in the localization and intensity of the pathologic process. It may remain stationary and limited to the cutaneous surface for many years, or it may be progressive at the outset and gradually involve the viscera, including the central nervous system. The case to be described belongs to the latter category and illustrates unusual localization of neurofibromas.

E. B., aged 21, for a number of years has had multiple small, very small and large sessile tumors disseminated over the surface of the body, face, thorax, dorsum and extremities. Six or seven years ago external deviation of the left eye developed. Soon afterward palsy of the left side of the face, of the peripheral type, appeared. Several months ago he began to experience difficulty in walking, standing or turning while standing.

The patient now shows pronounced neurofibromatosis, with tumors of different sizes spread over the body, two of which have unusual locations, namely, on the tongue and in the eyebrow. There is also marked involvement of the central nervous system—the third and seventh cranial nerve and the spinal cord—producing abolition of all reflexes in the lower extremities.

Comment.—The gait, station, loss of tendon reflexes and suspected muscular atrophy of the lower limbs suggest, clinically, multiple neuritis and, pathologically, tumors on the peripheral nerves or nerve roots. Conditions of this kind have been observed, but in all such cases one would expect pain. However, instances have been reported in which pain was absent in spite of the presence of multiple neurofibromas on the meninges and the roots and trunks of the nerves. Cases have been observed in which there was compression from neurofibromas in the cerebellopontile angle, on the sciatic nerve or in the spinal cord without sensorimotor manifestations. In the present case there are motor manifestations with areflexia, but no sensory symptoms, either subjective or objective. The bilateral foot drop in this case is only partial. The Romberg sign is pronounced. Amyotrophy is generalized and only apparent, being distributed equally over the body; it cannot be considered as myelopathy. Besides, there is no reaction of degeneration. The absence of the knee and achilles jerks is not in keeping with the incomplete clinical picture of multiple neuritis. For all these reasons, one is led to believe that the spinal cord is incriminated and that extramedullary tumors are compressing the lumbosacral segment of the cord. Involvement of the base of the brain by a tumor at the upper and another at the lower border of the pons, compressing the third and the seventh nerve, respectively, on one side, places the case among those of the encephalomedullary form of neurofibromatosis.

In consideration of the common embryonic origin of the skin and the nervous system, one must view neurofibromatosis as a systemic neuro-ectodermal disease. The tumors in this disease originate by cellular proliferation in the membrane of Schwann, which was considered by Held and Nageotte to be peripheral neuroglia. Recklinghausen's conception of the tumor was that of fibrous proliferation of the perineurium. As to the pathogenesis of the disease process: Some authors have thought that it is due to an endocrine disturbance. Adrian, Merk, Kawashima and others observed pathologic alteration of the adrenal glands in cases of neuofibromatosis. Defective development of the ovaries has also been noted. Other investigators have expressed the opinion that all such endocrinal disorders repercuss on the hypophysis, with neurofibromatosis as the final result.

DISCUSSION

DR. J. W. MCCONNELL: Is there no doubt that the tumor of the tongue is of the same type as the other tumors?

DR. ALFRED GORDON: The tumor of the tongue is of the same type as that in the neck and is painless. One may have symptoms of multiple neuritis and have no pain along nerve trunks. The patient is only 21; he is not suffering particularly. Hearing is not interfered with.

DR. R. S. WIGTON: In the medical and neurologic services at the Hospital of the University of Pennsylvania 15 cases of neurofibromatosis have been seen in recent years. In 12 of the 15 cases involvement of the central nervous system was indicated. Involvement was proved in 6 of the 12 cases and was presumptive in 6. Of the 6 instances in which it was proved, there were bilateral acoustic neurofibroma in 3, unilateral acoustic neurofibroma in 1, a tumor of the brachial plexus in 1 and a fibroblastoma of the spinal cord in 1. In all 6 presumptive cases there were signs of involvement of the nerves to the lower extremities, and in 4 the eighth nerve appeared to be affected.

Dr. Gordon's presentation is significant; although much has been written about the manifestations of Recklinghausen's disease, the high incidence of involvement of the central nervous system deserves further mention. It must be true that in many cases minimal symptoms referable to the central nervous system may be passed by on medical examination and their prognostic significance overlooked. Likewise, in cases in which symptoms of involvement of the central nervous system are primary, minimal signs of generalized neurofibromatosis may be overlooked, and a valuable aid to treatment and prognosis may be missed through failure to associate the neurologic disease with neurofibromatosis. In all cases of vague involvement of the lower limbs, tumor of the spinal cord and slowly progressive involvement of the eighth nerve, particularly if bilateral, neurofibromatosis should be considered.

DR. G. D. GAMMON: I have been interested in the manifestations of this disease other than those involving the central nervous system and skin. In 4 of the cases discussed by Dr. Wigton there was evidence of involvement of bone. This is not to be confused with Recklinghausen's disease of the bones, which is due to hyperparathyroidism. Slides illustrating various lesions of the bones are shown.

In neurofibromatosis the type of bone involvement consists of: (1) scoliosis, which Dr. Gordon's patient shows; (2) tumors of the periosteum and subperiosteal cysts, and (3) sarcomatous changes in the neurofibromas, with metastasis to bone. It has been stated that a tumor of the superior mediastinal nerve is more apt to become malignant than neurofibromas elsewhere in the body. The incidence of involvement of bone is about 25 per cent.

Only in the past few years is it becoming recognized that neurofibromatosis is a generalized systemic disease, involving the skin, the nervous system and the bones, and that it is associated with congenital defects. The disease tends to progress, and, curiously, the effect of pregnancy and puberty is marked. The effect of pregnancy is so pronounced that Dr. J. J. Eller, of New York, has recommended sterilization for women who show this accelerated growth.

DR. ALFRED GORDON: In the literature at my disposal a number of cases were reported of small tumors along the nerve trunks; the patients, nevertheless, experienced no pain, although in the majority of such cases there is bound to be pain. My patient has never experienced pain. No portion of the central nervous system is exempt from invasion in Recklinghausen's disease.

OCULAR DISTURBANCES ASSOCIATED WITH EXPERIMENTAL LESIONS OF THE MESENCEPHALIC CENTRAL GRAY MATTER, WITH SPECIAL REFERENCE TO VERTICAL OCULAR MOVEMENTS. DRS. E. A. SPIEGEL and N. P. SCALA, Washington, D. C.

This article appeared in the October 1937 issue of the *Archives of Ophthalmology*, page 614.

DISCUSSION

DR. J. C. YASKIN: It is well known that in cases of tumor (medulloblastoma) of the vermis nystagmus, especially of the vertical type, is frequent and helpful in diagnosis. How do the authors correlate their experimental data with this symptom?

DR. E. A. SPIEGEL: I think that vertical nystagmus associated with tumor of the vermis is a symptom of involvement not of the midbrain but of the cranial part of the vestibular nuclei. One obtains rotary nystagmus from the most caudal portion, horizontal nystagmus from somewhat more anterior parts and vertical nystagmus from the cranial part of the vestibular nuclei. The results of these experiments on animals can be applied to the human brain (Leidler and Marburg).

HABITUATION TO MARIJUANA: A NEW ADDICTION. DR. N. S. YAWGER.

While the plant is known in history as hashish and in the recent Congressional act as marijuana, the scientific name is Cannabis sativa. Its widespread growth and important commercial uses may to some extent hamper law enforcement. From marijuana's fiber twine, rope and bags are made. It yields a rapidly drying oil, which is useful as an ingredient of paints and varnishes; this oil is also used in the manufacture of soaps and linoleum. Birds thrive on the seed. Therapeutically, marijuana has been employed to relieve pain in migraine, to overcome nervousness and to produce euphoria; but the drug now is seldom used, owing in part to the great variability in potency. As an aphrodisiac it may be active at first but, like opium, this effect diminishes with subsequent addiction. While the subject is under its influence things long forgotten may be recalled in detail, an effect that invites careful research. Preparations of the plant may be smoked, chewed or drunk, but in the United States indulgence is mostly through cigarets, known in slang as "reefers." Marijuana differs from such habit-forming substances as opium, cocaine and alcohol; although often entrancing, it does not enslave with moderate use, so that it may be discontinued; from a "drunk" there are no hangover symptoms and no known fatalities. Its moderate use, however, is not without danger: With characteristic indiscretion, the adolescent may be eager to experience the thrill offered by this new kind of cigaret, and the well known action on perception, the lengthening of time and space, may prove disastrous if the smoker is driving a car. When the drug is used daily in large quantities, the direct action on the cerebrum often causes chronic mental deterioration, an effect which has been demonstrated for ages, notably in India and Egypt. During the last ten years the use of marijuana has been growing steadily in the United States, and many lurid and startling headlines in the public press have told of its dangerous, crime-producing effects—homicides, suicides and assaults, including those of a sexual type. However, competent observers do not believe that it is often the direct cause of crime. Actually, there is lessening of the devotee's power of inhibition, thereby leaving harmful tendencies unrestrained but, as such, marijuana probably is not as great a menace as alcohol.

DISCUSSION

DR. J. C. MUNCH (by invitation): The difficulties which have been pointed out by Dr. Yawger are well known. I may refer to the hearing before the House Committee on Ways and Means, in connection with H. R. 6906, which was signed by President Roosevelt on Aug. 2, 1937.

It is not difficult to identify cannabis. It grows along the roadside. The plants grow from 3 to 15 feet (0.9 to 4.5 meters) in height. The type imported from India has an entirely different appearance—the leaves are brownish and stick together in lumps. The kind grown in the United States looks like hay. The material used in the "reefers" is prepared from the American cannabis. The Indian specimen cannot be imported without special permission. It has not been

feasible, therefore, to bring much into the country. The American specimen has all the desired medicinal effect.

Is there any current medicinal use for cannabis? Dr. W. C. Woodward, of the American Medical Association, expressed the belief that no legislation should be passed which would interfere with the right of the physician to do as he pleased and to prescribe whatever he sees fit. Cannabis, when added to salicylic acid and other drugs for the manufacture of corn plasters, has been used for a long time. It was believed that cannabis had a local analgesic effect. Study showed this is not so—it increases rather than decreases local sensitivity. In treatment for tetanus or rabies it was used at one time to make the last hours more comfortable—there is now a better treatment. There does not seem to be any medicinal use for cannabis at this time.

Philadelphia had the unenviable reputation of having destroyed 200,000 pounds (9,080 Kg.) of cannabis last fall. The photographs presented (by permission of Dr. John Remig) illustrate the appearance of the product. It can be detected when used with tobacco ("reefers," or cigarets). The use of cannabis alone or in conjunction with diacetyl morphine (heroin) or cocaine for doping horses, dogs or human subjects has received a good deal of attention (perhaps more than it is entitled to).

Cannabis may be prescribed for patients. The section of narcotic regulations goes into great detail on this point. One observes the same "ritual" as in prescribing morphine. A license is necessary to issue and fill the prescription. Under the tax act of 1937, if it is found that the holder is without a license, he can be fined $100 for every ounce on hand.

Cannabis has received international consideration, particularly by the Subcommittee on Opium of the League of Nations. It decided that cannabis has become World Public Enemy No. 1. Opium has been brought under contral, but cannabis is worse. Agitation has led to the tax act of 1937, and similar legislation will be enacted by every civilized nation of the world.

DR. ALFRED GORDON: I wish to ask Dr. Munch whether Coca-Cola contains cocaine.

DR. M. W. THORNER: About three or four years ago Drs. Lindemann and Malamud, of the University of Iowa, investigated the psychologic effects of intoxicating drugs, including cannabis (*Am. J. Psychiat.* **13**:853 [Jan.] 1934). I cite this reference because of Dr. Yawger's suggestion that cannabis may be used by psychiatrists for the purpose of rendering patients more communicative. Roughly, the work of Drs. Lindemann and Malamud suggested that other, more innocuous drugs, such as sodium amytal, may be used for essentially the same purpose.

DR. J. C. MUNCH: In the famous case of the United States versus the Coca-Cola Company, started more than twenty years ago, it was found that Coca-Cola at that time was made from coca leaves which had not been decocainized, and it was assumed they might contain cocaine. However, the composition was changed so that, while it is true that at this time an extract prepared from coca leaves is used as a basis for Coca-Cola, there is no cocaine in the Coca-Cola of today.

DR. N. S. YAWGER: All are grateful to Dr. Munch, who is a world authority on these subjects, for giving some of his experiences.

PHYSICOCHEMICAL STUDIES OF THE CEREBROSPINAL FLUID. DR. MONA SPIEGEL-ADOLF.

Combinations of methods for the determination of conductivity and interferometric valves, alone or in conjunction with analytic determinations, have been used as new means of approach to investigation of the cerebrospinal fluid. For 156 samples of cerebrospinal fluid from patients with neurosurgical conditions (Dr. Temple Fay's service) and from neurologically normal patients (Dr. William Babcock's service), the electrical conductivity and interferometric values were measured according to classic methods. The same specimens of cerebrospinal

fluid were tested also for their protein and sugar contents. With the help of self-made graphs, it is possible to find the concentration of sodium chloride which corresponds to the measured conductivity of the cerebrospinal fluid and to compute graphically the interferometric value belonging to this concentration of sodium chloride. This value (IE) represents the interferometric value contributed by the electrolytes of the cerebrospinal fluid. When this value is deducted from the total interferometric value of the cerebrospinal fluid, the resulting difference represents the interferometric value of the nonelectrolytes INE. The ratio $\frac{INE}{IE}$ is independent of accidental changes in concentration of the cerebrospinal fluid. Therefore, changes in the ratio of $\frac{INE}{IE}$ indicate changes in the composition of the cerebrospinal fluid. The nature of these changes can be elucidated to a certain extent by expressing the protein and the sugar content of the cerebrospinal fluids in terms of the interferometric values (which can be done graphically) and by deducting these values from the respective interferometric values for nonelectrolytes (INE). The resulting residual interferometric value (RIV), when it is higher than normal, indicates the presence of increased amounts of lipoids and protein and lipoid cleavage products. This may be due partly to tissue cleavage and partly to increased permeability of the barrier between the blood and the spinal fluid. The INE ratio and the residual interferometric value were computed in all cases. The material was divided into four groups according to its origin. The lowest figures for the $\frac{INE}{IE}$ ratio and the residual interferometric values were observed in group 1 (surgical conditions, hysteria and headache), and the highest, in group 4 (tumors of the brain). The values for group 2 (neurologic diseases) and group 3 (convulsive disorders) came between these extremes. The behavior of the cerebrospinal fluid in cases of convulsive disorders is of special interest, since the average protein content was normal. The 60 cases of convulsive disorders were classified according to the severity of attacks and the duration of the condition. The highest figures for the $\frac{INE}{IE}$ ratio and the residual interferometric value were found in cases of grand mal attacks lasting for several years or becoming worse and associated with mental deterioration. The lowest values were shown in cases of symptomatic convulsions, while values in cases of mild petit mal, genuine epilepsy in which improvement was shown and convulsive states in babies came between these extremes. The parallelism between the intensity and frequency of the convulsions and the height of the $\frac{INE}{IE}$ ratio points to convulsions as the cause of the changes in the cerebrospinal fluid. This view is supported by recent findings for patients with dementia praecox in the neuropsychiatric division of the Philadelphia General Hospital in whom, for therapeutic reasons, convulsions had been induced. In most of these cases there was a marked increase in the $\frac{INE}{IE}$ ratio after convulsions. On the basis of recent experiences with syphilitic patients who were subjected to repeated spinal tap, it is improbable that the repeated lumbar punctures alone were responsible for the total increase in the $\frac{INE}{IE}$ ratio observed in schizophrenic patients undergoing convulsive therapy. As expected, the $\frac{INE}{IE}$ ratio and the residual interferometric values are increased above the group average for xanthochromic fluids and fluids giving a positive colloidal gold reaction. In 6 cases lumbar puncture was repeated in the course of the disease. The results point to a possible prognostic significance for changes observed in the $\frac{INE}{IE}$ ratio and the residual interferometric value.

Book Reviews

Das Corpus Geniculatum: Eine anatomische-klinische Studie (Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie, vol 62). By M. Balado and E. Franke. Paper. Price, 36 marks. Pp. 116, with 123 illustrations. Berlin: Julius Springer, 1937.

This monograph may well stand as a model of modern anatomic investigation of a small but important structure. The purely descriptive portion of the treatise consists of an adequate description of the embryologic development of the region, a clear account of its gross anatomic relationships, a description of the cell types and arrangement of fibers and a comparison of the form and relation of the nucleus in various primates. Especially to be commended is the extensive use of reconstructions, which give a new and illuminating conception of the three dimensional form and relationships of the five cell layers which comprise the structure. The blood supply is given merited attention.

Of particular interest to the neurologist is the description of the functional anatomic relations and fiber connections of the corpus geniculatum. This is based on a critical review of the literature and the study of twenty-one cases in which there were lesions of the optic connections. The changes in the visual field were studied by quantitative perimetry during life, and the autopsy material was prepared in serial sections, permitting an accuracy and certainty of observation heretofore attained only in scattered instances.

The general conclusions of Hippel and Rönne were confirmed as to the location in the optic nerve of fibers from the macula. They lie first in the lower temporal quadrant of the nerve and later shift to a central position about the point of entry of the retinal vessels. In the chiasm the fibers from the temporal half of the macula cross at the posterior border. In the optic tract the fibers from the two maculae unite still to lie between the fibers representing the upper half of the retina mesially and those representing the lower half laterally. This relationship persists in the corpus geniculatum itself. The fibers from the macula end in the frontal pole and body of the geniculate body. This confirms Rönne's observations. The fibers from the upper and the lower quadrant end in the mesial and the lateral posterior portion, respectively. The particular layers in which each portion of the tract ends are given, with an extraordinary minuteness of detail. The experimental observation of Minkowski that fibers from homologous portions of the two retinas end in superposed cell layers in the corpus geniculatum is confirmed in human material for the first time.

While the optic radiation receives only brief consideration, a few important points stand out clearly. The radiation corresponds to the external sagittal stratum, as maintained by Pfeifer and others in opposition to Monakow. In several cases small degenerations could be traced in a horizontal direction from the corpus geniculatum to the cortex, demonstrating that the upper margin of the striate area is connected through the upper portion of the radiation with the anteromesial portion of the geniculate body and corresponds to the upper portion of the retinal halves. The authors refer to evidence which they have already presented that the macula must be represented throughout a large portion of the striate area, but whether partly or wholly at the occipital pole is not yet clear. They mention an important case which bears on the question of the alleged "double representation" of the macula; hemianopia extending to the fixation point was found in a case in which softening had destroyed the striate cortex but left the radiation intact. The corresponding geniculate body showed profound retrograde degeneration throughout, which would be difficult to explain if the axons of any of its cells extended to the opposite cortex.

The pregeniculate gray matter and the lower giant cell layers of the geniculate body are also considered. They probably are not concerned with primary visual impressions, for they do not degenerate after lesions of the tract, the radiation or the pathways to the colliculi.

Digestion and Health. By Walter B. Cannon, M.D. Price, $2. Pp. 160, with 14 illustrations. New York: W. W. Norton & Company, Inc., 1936.

In this short volume the author has described concisely and clearly a number of observations on the neurophysiology of the digestive tract. His first chapter deals with the specific nature of the gastric motility producing hunger and thus contrasts hunger with the more general bodily sensation appetite. Factors which enhance and diminish the objective hunger contractions are emphasized. In the second chapter he discusses the dependence of thirst on localized dryness in the pharynx and points to lines of evidence from which one is led to conclude that thirst is largely dependent on failure of salivation. The sensation of thirst as it is found after acute hemorrhage, during the postprandial period and in acute crises of anxiety is explained on this basis.

The third chapter deals with the role of the two principal divisions of the autonomic nervous system in maintaining the tonus of the smooth musculature of the gastro-intestinal tract and with their relative unimportance in relation to peristaltic movements. Specific processes discussed are the act of swallowing, receptive relaxation of the stomach during swallowing, the rate of movement of the intestinal contents and the act of defecation. The fourth chapter has to do with forms of indigestion and other gastro-intestinal symptoms which result from pain, worry and excitement. Gastric stasis, spastic constipation and diarrhea are cited as examples. The rest of the chapter is concerned with illustrative cases and with observations on the role of the autonomic nervous system and the adrenal glands in the maintenance of bodily homeostasis—a sort of apology for the existence of the neurovegetative system, with its frequent inconveniences.

The book as a whole is a brief, well documented review of a series of observations on the gastro-intestinal tract which have an immediate application in the understanding and treatment of illnesses characterized by disordered function. While it is a little too technical for the layman, the book is written in a simple, expository style and should serve excellently to review this borderline field for those primarily interested in the many related branches of medicine.

Vom Bau und Leben des Gehirns. Verständliche Wissenschaft, Band XXXI. By Ernst Scharrer. Price, 4.80 marks. Pp. 168, with 81 illustrations. Berlin: Julius Springer, 1936.

This is the thirty-first volume of a popular science series, entitled "Verständliche Wissenschaft." It attempts to present to the reader a concise statement of the known facts about the development, structure and function of the nervous system—central, peripheral and vegetative. It is not clear whether the little book is addressed to the uninformed layman, the undergraduate student or the physician in medical practice. Certain it is that none of these possible ends could be served with profit by the booklet as it is. The presentation is too compact for the uninitiated, too meager in scope as a source of information for the struggling student and too elementary for the graduate physician in quest of reinstruction.